American Institute of Integrative Oncology
RESEARCH & EDUCATION

Foundations of Integrative Oncology
COURSE

GRAND ROUNDS CALL
With Dr. Nalini Chilkov
March 14th, 2018

Second Wednesday of Every Month (unless noted otherwise)
5:30 PM Pacific / 6:30 PM Mountain / 7:30 PM Central / 8:30 PM Eastern

Clinical Pearl: Adaptogens for Cancer Related Fatigue

Adaptogen: Enhances the nonspecific ability to assist the body to withstand withstand stress and maintain normalcy even when threatened with pathological conditions.

Ginseng and Cancer Related Fatigue
Dose 2000 mg/day x 8 weeks (Barton et al, 2013)
Dose 800 mg orally daily x 29 days (Yennurajalingam et al, 2015)

Purified Extract of Astragalus (Huang Qi)
PG2 is a bioactive extract of A. membranaceus which is believed to improve palliative treatment in advanced cancer patients. In advanced cancer patients, PG2 is safe and effective botanical-derived drug.

Patients with advanced cancer & moderate to severe CRF (Chen et al, 2012)
- 82% reported improvement after 4 weeks
- 71 % of non responders reported improvement after the 2nd 4 week cycle
- No major or irreversible toxicities were observed

Ginseng and Astragalus Formula
Bu Zhong Yi Qi Tang | Hochu-ekki-to
Dose: 2.5g tid (Jeong et al, 2010)
- Statistically significant decreased fatigue levels were observed within 2 weeks
- Scales for assessing overall QOL also improved
- No serious adverse effects occurred
- Inhibition of TNFa, IL6, IL1, IFg

Ganoderma lucidum - REISHI Ling Zhi
Dose: 3-5 g/day (Liao, Apaya & Shyur, 2013)
- Used to treat cancer-related fatigue in breast cancer patients undergoing endocrine therapy
- Improved physical well-being, less fatigue, less anxiety and depression, and overall better QOL
- Immunomodulatory, antioxidative, antimetastatic, and antitumor effects
- Anti-proliferative, pro-apoptotic, induces cell cycle arrest
- Adjuvant for hepatoprotection in cancer therapy
- Statistically significant improvement in TNF-α, IL-6, and liver and kidney function

Withania somnifera (Ashwagandha) (Biswal et al, 2013)
Dose: 1-3 g/day
- Improvement in Quality of Life and Cancer Treatment Related Fatigue
- Improvement in trend of Overall Survival.
- Protect Bone Marrow from chemotherapy-induced hematotoxicity
- Improvement in White Cell Count
- Enhanced Radiosensitization
- Improved Sleep patterns, Responsiveness, Alertness, and
- State of Awareness + Physical Capabilities

Clinical Question: Xi-Huang-Wan

Ana Komazec: What has been your experience of using Xihuang Wan in clinical application? I have come across the research article from last year:

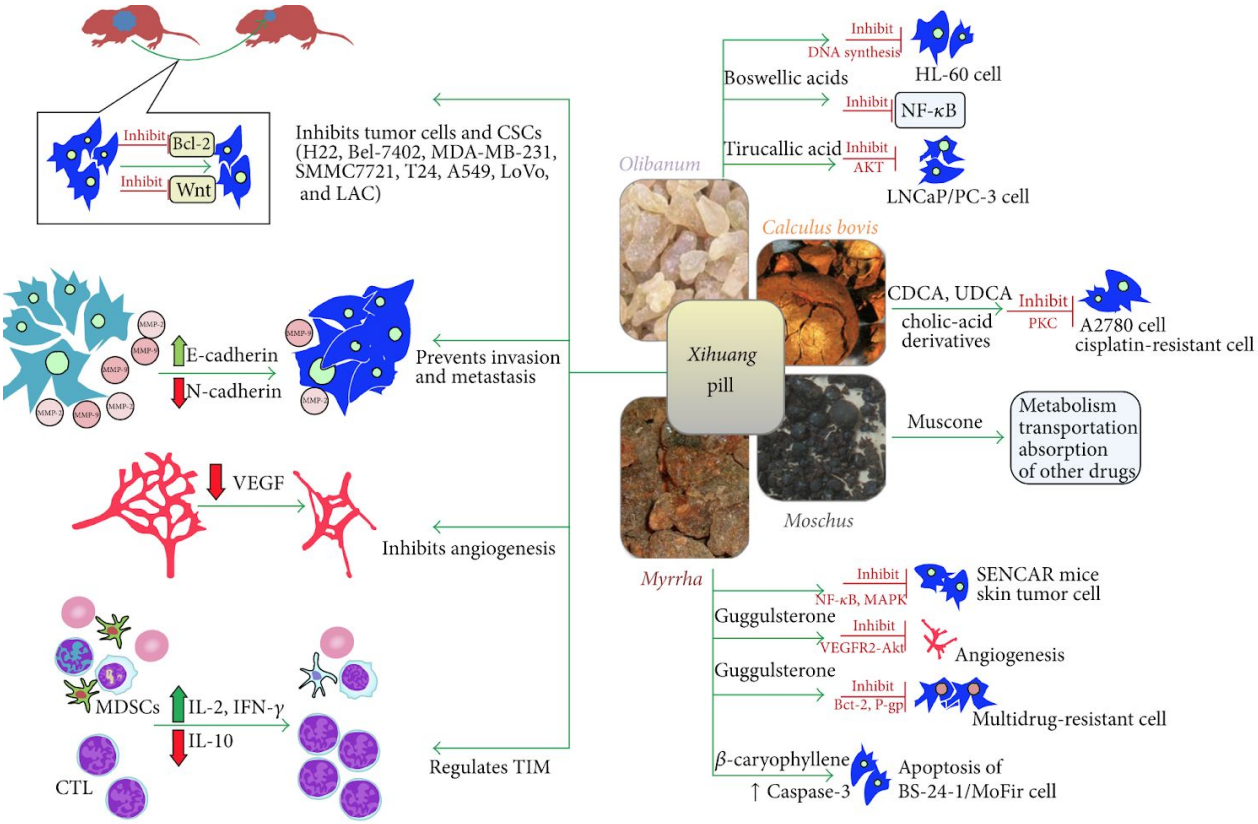
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5387817/
Proposed mechanism : https://www.hindawi.com/journals/ecam/2015/854307/fig1/

"XH can also inhibit the growth of tumor cells and cancer stem cells, prevent tumor invasion and angiogenesis, and regulate the tumor microenvironment."

Dr. Nalini:

Xi-Huang-Wan (XHW) was prepared by a well-known Chinese physician Hongxu Wang during the Qing dynasty. It contains four herbs including:

- **Bos Taurus domesticus Gmelin, Bovine Gall Bladder (bile salts)**
- **Boswellia carterii Birdw, Boswellia (Frankincense)**
- **Commiphora myrrha Eng1, and Myrrh**
- **Moschus. Deer Musk**



Xi-Huang-Wan has been used to treat several malignant cancers including **liver cancer** in the past and still serves the purpose. Further studies have shown that it can **inhibit the expression of bcl-2, c-myc, and enhance the expression of p53 acting on Bel-7402 cell line, which may be related to cancer cell apoptosis.**

There are many Chinese herbs or herbal formula that are used in the treatment of cancer. Compared with conventional western medicine in the treatment of cancer, the advantage of Chinese herbal therapy are:

1. **The treatment of cancer is holistic.** The herbs work not only to prevent the cancer growth in local spot, but also improve the ability of the defense system of the whole body, so that to prevent any new growth of cancer in any other part of the body and to prevent the spread of the current cancer cell to grow in other part of the body.
2. **Treat the cancer and the symptoms at the same time.** With conventional medicine, chemotherapy or radiation therapy can cause side effects, such as bleeding, frequent infection, poor appetite, nausea, vomiting,

constipation/diarrhea, chronic fatigue. To solve these symptoms, additional chemical drugs are needed. With Chinese herbal therapy, the symptoms due to the cancer and/or to the therapies are solved at the same time.

3. **Treat the cancer without affecting the body's normal ability.** As mentioned, standard chemotherapy or radiation therapy damages the defense system of the body. While the Chinese herbal therapy, by improving the overall body condition, actually improves the defense system of the body, so that there is much less chance for patients to get new or additional infections during the treatment.
4. **Chinese herbal therapy is much safer. The side effect rate is very low.**
5. **Chinese herbal therapy is much less expensive than conventional chemotherapy, radiation therapy or surgical therapy.**

Resource: https://www.acupuncture123.ca/E11_Xihuang_wan_edmonton.html

Xihuang wan

Function in Chinese herbal therapy: To detoxify, to clear Fire, to reduce swelling (the cancer size). Supply Qi and Blood in the body, improve blood micro-circulation.

Function in terms of conventional medicine: Reduce side effects due to chemotherapy and radiation therapy; to improve function of bone marrow in production of blood cells; to increase appetite, keep body weight.

Functions to battle against bacteria, suppress infection reaction, to reduce pain. Activate function of microphages, NK cells, T lymphocyte cells.

Prevents the activity of blood vessel production factors, stops new blood vessel growth in the cancer tissues. Increase the number of T cells and IgM.

Lab tests also suggest that the Xihuang wan works to prevent the growth the various cancer cells in culture conditions.

Ingredients: Niuhuang, Shexiang, Ruxiang, Moyao.
Clinic use:

- **Various cancers**: it has been used in the treatment of breast cancer, cervical cancer, bladder cancer, liver cancer, lung cancer, esophagus cancer, stomach cancer, thyroid cancer, colon cancer, leukemia, etc.
- **Various suppurative and proliferative diseases**, such as Mammary gland hyperplasia, breast fibroma, lymphatitis, osteomyelitis, and sepsis, chronic appendicitis, acute or chronic mump, Erysipelas, herpes roster, pyoderma, lymphatic tuberculosis, etc.

References:

Review on the Applications and Molecular Mechanisms of Xihuang Pill in Tumor Treatment
Guo, Q., Lin, J., Liu, R., Gao, Y., He, S., Xu, X., ... & Bao, Y. (2015). Review on the applications and molecular mechanisms of Xihuang pill in tumor treatment. Evidence-Based Complementary and Alternative Medicine, 2015.

Clinical Effects of Xihuang Pill Combined with Chemotherapy in Patients with Advanced Colorectal Cancer
Yu, D., & An, G. Y. (2017). Clinical Effects of Xihuang Pill Combined with Chemotherapy in Patients with Advanced Colorectal Cancer. Evidence-Based Complementary and Alternative Medicine, 2017.

Application and Perspectives of Traditional Chinese Medicine in the Treatment of Liver Cancer
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Application and Perspectives of Traditional Chinese Medicine in the Treatment of Liver Cancer
Mao, X., Zhang, Y., & Lin, N. (2015). Application and perspectives of traditional Chinese medicine in the treatment of liver cancer. Cancer Translational Medicine, 1(3), 101.

Case Study: The Tumor Microenvironment: Biomarkers of an Advanced Colorectal Cancer Patient

Patient Caucasian Male Stage 4 Colorectal Cancer - Provided by Dr. Chilkov

Background: The Tumor Microenvironment-Cancer Terrain: Stage 4 Colorectal Cancer with Liver Metastasis

Red Flags (See attached LabCorp Report)

- Low Albumin: 1.1 (normal 1.2-2.2) - early sarcopenia and cachexia and altered protein metabolism
- Elevated Liver Function Tests: Alk Phos 242 H (39-117). ALT 62 (0-44)
- Low Serum Iron 33 Low. (38-169)
- Low Iron Saturation 11% Low (15-55)
- C677T Single DNA MTHFR Mutation - indicator of detoxification
- Transforming Growth Factor beta1 7007 High (867-6662)
- CEA 7.5 H (0-4.7)
- CA 19-9 1223 H (0-35)
- hs-CRP 84.02 (0-3.0)
- Interleukin-6 13.2 H (0-12.2)
- GGT 210 H (0-65)
- Ceruloplasmin 41.8 H (16.0-31.0)
- Copper (high normal) 159 (72-166)
- Zinc 92 normal (56-134). Low Zinc to Copper Ratio. 1:1 or 2:1 is protective
- Fibrinogen activity 483 (high normal) 193-507.
- Neutrophil: Lymphocyte Ratio 57:19 = 3.0
- Low Creatinine 0.56 (0.76-1.27)
- Elevated CRP: Albumin Ratio. 84.2. : 3.9 21.6. (> 3.04 poor prognosis)
- Low Albumin: Globulin Ratio. 1.1 (improved survival >1.29)

Clinical Questions & Answers

Live Question: What would be the dosages of quercetin, milk thistle, L-carnitine per day in the Therapeutic Shake?

Dr. Nalini:

- Refer to the Materia Medica module for dosing recommendations
- Milk thistle: 3 grams daily of high quality powder or extract; may use up to 5 grams for a patient with high liver markers
- Quercetin: 2 grams per day (best absorbed with proteolytic enzymes)
- L-Carnitine: 1-2 grams per day; may use up to 4 grams in divided doses for patient with sarcopenia and cachexia

Live Question: What supplements and other things would you recommend to reduce fluid from ascites associated with ovarian cancer?

Dr. Nalini:

- Ascites is driven by tumor load in the liver or the peritoneal cavity, capillary leakage of fluid into the peritoneal cavity
- Fluid is removed by physician as needed. Generally not a reversible condition, part of end stage disease

Live Question: What about constipation?

Dr. Nalini:

- Identify the cause of constipation with a thorough assessment and treat responsibly. Never treat the symptom. Do a thorough assessment to understand etiology and treat within a functional medicine framework.
- Basic support: adequate hydration, fiber, healthy microbiome
- Safest approach: Magnesium citrate (300-500 mg with 8 oz of water)

- Adhesions: soften connective tissue and improve lymphatic flow with castor oil packs over pelvis and abdomen, Boswellia, proteolytic enzymes
- Low or loss of peristalsis due to surgery or opioid use: keep stool soft, low residue diet, acupuncture and moxibustion Acupoints ST36 LI4, LI10, LI11, ST25
- Chemotherapy-induced liver congestion: Support liver detoxification function: milk thistle, n-acetyl cysteine (NAC), Designs for Health Detox Antiox, NATURA Cell Guardian
- Never use detox promoting supplements during chemotherapy These supplements must be timed to avoid drug interactions and interference with drug metabolism
- Acupuncture points LIV3 and LI14

Live Question: One of my patients was asking about acacia fiber?

Dr. Nalini:

- Acacia fiber is a type of soluble fiber
- Designs for Health Paleofiber is a multifaceted formula that provides soluble and insoluble fibers, prebiotics and probiotics to promote healthy microbiome

Live Question: A patient is feeling full after eating and has slow digestion. It could be a side effect of receiving chemotherapy treatment. A CT scan is not showing any signs of obstruction or growth. Is this something you've seen?

Dr. Nalini:

- Consider why is the patient having the symptom? Assess etiology first.
- Complete a deeper assessment to determine what is going on to make an informed decision about what is an appropriate and safe intervention
- Consider the frequency, duration and location to understand the etiology
- Communicate with the patient's oncology team

March is Colorectal Cancer Month

Dr. Tina Kaczor ND - Expert in colorectal cancer

- Educate patients about screening and risk factors
- Routine screening with a colonoscopy begins at age 50. The results along with risk factors will help determine frequency of ongoing screenings.
- Stool testing is another screening tool (Leading edge stool test: Cologuard - https://www.cologuardtest.com)
- 1 in 20 people in the United States will get colorectal cancer. It is less likely to occur in women.
- Third most diagnosed cancer in the United States
- Most deadly cancer after lung cancer
- High recurrence rate
- Risk factors: over 50 years of age; having an immediate family member diagnosed earlier than 55 years of age doubles risk factor.
- Modifiable risk factors: eating red meat, altered microbiome, excessive alcohol intake, poor diet (diets low in fiber, colorful fruit and vegetables) sleep disruption, obesity, chronic inflammation, sedentary lifestyle
- Supplements for a healthy colon: probiotics, prebiotics, fish oil (1-3 g per day), curcumin (1-2 grams per day), optimize vitamin D, and adequate selenium, folic acid and calcium in diet
- Some grains are encouraged to provide soluble plant fiber to establish a healthy microbiome. (Paleo diets often lead to too little soluble fiber substrate to promote a vital microbiome)

Study Highlight: Many Breast Cancer Patients are not Receiving Genetic Evaluations

Attached. This study discusses how all breast cancer patients should have their genetic markers, receptor types and BRCA gene mutations evaluated as part of a the standard of care and a thorough work-up.

New Research: Optimal Duration of Extended Adjuvant Endocrine Therapy for Early Breast Cancer; Results of the IDEAL Trial (BOOG 2006-05)

Blok, E. J., Kroep, J. R., Meershoek-Klein Kranenbarg, E., Duijm-de Carpentier, M., Putter, H., van den Bosch, J., ... & Rutgers, E. J. T. (2018). Optimal duration of extended adjuvant endocrine therapy for early breast cancer; results of the IDEAL trial (BOOG 2006-05). JNCI: Journal of the National Cancer Institute, 110(1).

Abstract Background The optimal duration of extended endocrine therapy beyond five years after initial aromatase inhibitor–based adjuvant therapy for postmenopausal women with hormone receptor–positive breast cancer is still unknown. Therefore, we conducted a clinical trial to compare two different extended endocrine therapy durations.

Methods In the randomized phase III IDEAL trial, postmenopausal patients with hormone receptor–positive breast cancer were randomly allocated to either 2.5 or five years of letrozole after the initial five years of any endocrine therapy. The primary end point was disease free survival (DFS), and secondary end points were overall survival (OS), distant metastasis–free interval (DMFi), new primary breast cancer, and safety. Hazard ratios (HRs) were determined using Cox regression analysis. All analyses were by intention-to-treat principle.

Results A total of 1824 patients were assigned to either 2.5 years (n = 909) or five years (n = 915) of letrozole, with a median follow-up of 6.6 years. A DFS event occurred in 152 patients in the five-year group, compared with 163 patients in the 2.5-year group (HR = 0.92, 95% confidence interval [CI] = 0.74 to 1.16). OS (HR = 1.04, 95% CI = 0.78 to 1.38) and DMFi (HR = 1.06, 95% CI = 0.78 to 1.45) were not different between both groups. A reduction in occurrence of second primary breast cancer was observed with five years of treatment (HR = 0.39, 95% CI = 0.19 to 0.81). Subgroup analysis did not identify patients who benefit from five-year extended therapy.

Conclusion: This study showed no superiority of five years over 2.5 years of extended adjuvant letrozole after an initial five years of adjuvant endocrine therapy.

References

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Jeong, J. S., Ryu, B. H., Kim, J. S., Park, J. W., Choi, W. C., & Yoon, S. W. (2010). Bojungikki-tang for cancer-related fatigue: a pilot randomized clinical trial. Integrative cancer therapies, 9(4), 331-338.

Liao, G. S., Apaya, M. K., & Shyur, L. F. (2013). Herbal medicine and acupuncture for breast cancer palliative care and adjuvant therapy. Evidence-Based Complementary and Alternative Medicine, 2013.

Yennurajalingam, S., Reddy, A., Tannir, N. M., Chisholm, G. B., Lee, R. T., Lopez, G., ... & Cohen, L. (2015). High-dose Asian ginseng (Panax ginseng) for cancer-related fatigue: a preliminary report. Integrative cancer therapies, 14(5), 419-427.

SELECTED ADAPTOGENS for Cancer Related Fatigue

ADAPTOGEN DEFINITION

Enhances the nonspecific ability to assist the body to withstand withstand stress and maintain normalcy even when threatened with pathological conditions

Ginseng and Cancer Related Fatigue

J Natl Cancer Inst. 2013 Aug 21;105(16):1230-8.
Wisconsin Ginseng (Panax quinquefolius) to improve cancer-related fatigue: a randomized, double-blind trial, N07C2.
Barton DL, et al

DOSE 2000 mg/day x 8 weeks

Integr Cancer Ther. 2015 Sep;14(5):419-27.
High-Dose Asian Ginseng (Panax Ginseng) for Cancer-Related Fatigue: A Preliminary Report.
Yennurajalingam S, Reddy A, et al

DOSE 800 mg orally daily x 29 days

Purified Extract of Astragalus (Huang Qi)

A novel infusible botanically-derived drug, PG2, for cancer-related fatigue: a phase II double-blind, randomized placebo-controlled study.
Chen HW, et al. Clin Invest Med. 2012 Feb 1;35(1):E1-11.

PG2 is a bioactive extract of *A. membranaceus* which is believed to improve palliative treatment in advanced cancer patients. In advanced cancer patients, PG2 is safe and effective botanical-derived drug.

Patients with advanced cancer & moderate to severe CRF
82% reported improvement after 4 weeks
71 % of non responders reported improvement after the 2nd 4 week cycle
No major or irreversible toxicities were observed

Ginseng and Astragalus Formula
Bu Zhong Yi Qi Tang | Hochu-ekki-to

2.5g tid

- Statistically significant decreased fatigue levels were observed within 2 weeks
- Scales for assessing overall QOL also improved
- No serious adverse effects occurred
- Inhibition of TNFa, IL6, IL1, IFg

Bojungikki-Tang for Cancer-Related Fatigue: A Pilot Randomized Clinical Trial

Integrative Cancer Therapies
9(4) 331–338

DOI: 10.1177/1534735410383170
http://ict.sagepub.com

Ginseng and Astragalus Formula
Bu Zhong Yi Qi Tang | Hochu-ekki-to

2.5g-3.0g tid

Radix Astragali Membranacei	(Huang Qi)	Milk Vetch Root
Radix Codonopsis Pilosulae	(Dang Shen)	Codonopsis Root
Radix Angelicae Sinensis	(Dang Gui)	Tang Kuei Root
Rhizoma Atractylodis Macrocephalae	(Bai Zhu)	Atractylodis Rhizome
Pericarpium Citri Reticulatae	(Chen Pi)	Aged Citrus Peel
Rhizoma Cimicifugae	(Sheng Ma)	Black Cohosh Rhizome
Radix Bupleuri Chinensis	(Chai Hu)	Hare's Ear Root
Radix Glycyrrhizae Uralensis	(Gan Cao)	Licorice Root
Rhizoma Zingiberis Off Recens	(Sheng Jiang)	Fresh ginger Root
Fructus Jujuba	(Da Zao)	Jujube Fruit

Ganoderma lucidum REISHI Ling Zhi 3-5 g/day

- **Used to treat cancer-related fatigue in breast cancer patients. undergoing endocrine therapy**
- **Improved physical well-being, less fatigue, less anxiety and depression, and overall better QOL**
- Immunomodulatory, antioxidative, antimetastatic, and antitumor effects
- Anti-proliferative, pro-apoptotic, induces cell cycle arrest
- Adjuvant for hepatoprotection in cancer therapy
- Statistically significant improvement in TNF-*α*, IL-6, and liver and kidney function

Evid Based Complement Alternat Med v.2013; 2013. PMC3694462
Herbal Medicine and Acupuncture for Breast Cancer Palliative Care and Adjuvant Therapy
Guo-Shiou Liao et al

Effect of Withania somnifera (Ashwagandha) on the Development of Chemotherapy-Induced Fatigue & QOL in Breast Cancer Patients.

1-3 g/day

Improvement in Quality of Life and Cancer Treatment Related Fatigue
Improvement in trend of Overall Survival.
Protect Bone Marrow from chemotherapy-induced hematotoxicity
Improvement in White Cell Count
Enhanced Radiosensitization
Improved Sleep patterns, Responsiveness, Alertness, and State of Awareness + Physical Capabilities

Integr Cancer Ther. 2012 Nov 9. Biswal BM, et al

Hindawi Publishing Corporation
Evidence-Based Complementary and Alternative Medicine
Volume 2015, Article ID 854307, 10 pages
http://dx.doi.org/10.1155/2015/854307

Review Article

Review on the Applications and Molecular Mechanisms of *Xihuang* Pill in Tumor Treatment

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Academic Editor: Olumayokun A. Olajide

Xihuang pill (XH) is a complementary and alternative medicine that has been used in traditional Chinese medicine (TCM) for the treatment of tumors since the 18th century. XH has clinical effects on non-Hodgkin lymphoma, breast cancer, gastric cancer, liver cancer, and bone metastasis. XH can also inhibit the growth of tumor cells and cancer stem cells, prevent tumor invasion and angiogenesis, and regulate the tumor microenvironment. XH is composed of *Ru Xiang* (olibanum), *Mo Yao* (*Commiphora myrrha*), *She Xiang* (*Moschus*), and *Niu Huang* (*Calculus bovis*). Some of the compounds found in these ingredients exert multiple antitumor effects and may synergize with the other ingredients. We aimed to summarize the clinical applications and molecular mechanisms of XH and its chemical composition. This review will provide potential new strategies and alternative perspectives for tumor treatments and basic research into complementary and alternative medicine.

1. Introduction

Xihuang pill (XH), also called *Xihuang Wan*, is a complementary and alternative medicine used for tumor treatment in traditional Chinese medicine (TCM) since the 18th century. XH was originally developed by Wang Weide and was recorded in the *Wai Ke Quan Sheng Ji* during the Qing dynasty. XH was used for noxious heat with blood stasis syndrome. The prescription contains four TCM ingredients: three blood-activating and stasis-eliminating compounds (*Ru Xiang* [olibanum], *Mo Yao* [*Commiphora myrrha*], and *She Xiang* [*Moschus*]) and a heat-clearing and detoxifying compound (*Niu Huang* [*Calculus bovis*]). XH was recorded to have effects on treating lung cancer, breast cancer, intestinal cancer, lymphomas, and lymph node metastasis of malignant neoplasms in ancient China.

TCM is very important to tumor treatment strategies in China [1]. TCM is accepted in China to enhance the antitumor effects of conventional therapies, reduce the toxicity of chemotherapy and radiotherapy, alleviate tumor-induced clinical symptoms and cancer pain, and prolong the survival time of postoperational and advanced-stage cancer patients [2]. XH is often used in East and Southeastern Asia countries as an adjunct treatment combined conventional tumor treatment methods such as chemotherapy. XH is usually administered orally in 3 g doses twice a day and sporadically has skin rashes or pruritus as side effects [3].

We aimed to review the antitumor research of XH in both clinical and basic aspects and summarize the antitumor mechanisms of the four components of XH. Prospects and development trends for the application and study of XH are also described. This review may provide new strategies and different viewpoints on tumor treatments and basic research into complementary and alternative medicine.

2. XH Has Antitumor Effects When Combined with Conventional Therapies

2.1. XH Enhances the Response Rate of Non-Hodgkin Lymphoma. Non-Hodgkin lymphomas (NHL) are a heterogeneous group of lymphoproliferative disorders originating in B-lymphocytes, T-lymphocytes, or natural killer (NK) cells. CHOP (cyclophosphamide, vincristine, doxorubicin, and prednisone) is a first line chemotherapy regimen for NHL, and recent studies indicate that treatment with rituximab and CHOP (R-CHOP) is more effective [4, 5].

When combined with CHOP, XH can enhance the response rate to chemotherapy and prolong survival. Wang et al. [6] randomly and equally divided 60 NHL patients into a treatment (CHOP with XH) or control group (CHOP only). The three-year survival rate in the treatment group was significantly higher than that in the control group (92% versus 78%, resp., $P < 0.05$). Furthermore, patients in the treatment group had a greater clinical improvement in symptoms (e.g., hot flashes or night sweats) and Karnofsky's performance scores (KPS). Since rituximab is not included in the medical insurance drug catalogue in some developing counties such as China, R-CHOP might result in a heavy medical burden to patients with NHL and their families. Therefore, XH could possibly enhance chemotherapy effects, relieve NHL related symptoms, and reduce medical burden.

2.2. XH Improves the Efficacy of Conventional Therapy and Regulates Immunity in Breast Cancer. Breast cancer is the most common malignancy in women and the second leading cause of cancer-related death [7]. TEC (taxotere, epirubicin, and cyclophosphamide) and CEF (cyclophosphamide, epirubicin, and fluorouracil) are the most commonly used chemotherapy regimens for breast cancer [8, 9]. Radiation therapies [10], targeted therapies [11, 12], and endocrinotherapies [13] are also recommended in specific situations.

XH has been shown to affect breast neoplasms. Hong et al. [14] explored the application of XH with TEC in patients with breast cancer and found that XH could significantly enhance the two-year survival rate and overall response rate in the treatment group. However, XH did not alter the side effects of TEC. Furthermore, XH regulated T-lymphocyte subsets and improved the immunity of breast cancer patients taking CEF [15]. Breast hyperplasia, especially of the columnar cells, is the earliest histologically identifiable lesion linked to cancer progression [26]. Aside from the tumor, XH can treat benign lesions such as breast hyperplasia and prevent transformation into malignancies [27].

2.3. XH Has Clinical Effects on Advanced-Stage Liver Cancer. Primary liver cancer (PLC) is characterised by high mortality rate and poor prognosis [28]. Early stage PLC patients can undergo hepatectomy and their overall survival rate is relatively higher than that of advanced-stage patients [29]. Radiotherapy [30], drug therapy (such as the multikinase inhibitor sorafenib) [31], and interventional treatment (radiofrequency ablation or interventional transcatheter arterial chemotherapy [TAC] with or without embolization) [32, 33] are choices for patients with unresectable or recurrent cancer.

Liu et al. [18] combined XH with TAC in advanced-stage PLC patients. Both the overall one-year survival rate and the short-term response rate in the XH combination group were superior to those in the TAC group. Case reports of stage IV PLC patients also indicate that XH could relive tumor-related symptoms such as cancer pain, fever, or abdominal distention [19, 20].

2.4. XH Enhances the Effects of Chemotherapy on Gastric Cancer. Gastric cancer (GC) is one of the leading causes of cancer death worldwide, although geographical variations in incidence exist [34–36]. Treatments for GC include chemotherapy (platinum drugs, fluorouracil drugs, taxanes, and camptothecin) [37], radiotherapy [38], surgery [39], endotherapy [40], and HER-2 targeted therapy [41]. However, the effects of conventional treatment are unsatisfactory, especially in the advanced stages [42].

XH was reported to effectively treat stage IV GC when combined with DCF (docetaxel, cisplatin, and 5-fluorouracil) and significantly enhance the short-term response rate compared with DCF alone (77.5% versus 55.0%, resp., $P < 0.05$) [21]. Although the effect is still limited, XH could be an effective adjuvant GC treatment.

2.5. XH Controls Cancer-Induced Bone Pain and Promotes the Effect of Zoledronic Acid on Bone Metastasis. Bone metastasis occurs frequently in patients with advanced-stage cancers, such as lung cancer and breast cancer [43, 44]. The main symptoms of osseous metastasis are cancer-induced bone pain (CIBP) and skeletal-related events (e.g., radiation to bone, spinal cord compression and fracture), which decrease quality of life and an increase mortality [45, 46]. Aside from inhibiting tumor cells, zoledronic acid, together with denosumab, is a possible therapeutic regimen for bone metastasis [47].

TCM was reported to have an effect on bone metastasis and CIBP control [48, 49]. Combined with zoledronic acid or used alone, XH could significantly relive the CIBP in patients with breast cancer. Furthermore, XH could mildly enhance the effect of zoledronic acid on bone metastasis and regulate immunity [16].

3. XH Can Relieve the Side Effects of Modern Therapies

Modern therapies provide effective ways to treat tumors but have some toxicities and side effects, such as chemotherapy-induced peripheral neurotoxicity [50], radiation-induced stomatitis [51], or endocrinotherapy-induced menopause-like syndrome [52]. XH could be effective in this field as a natural supplementary medicine. In fact, XH was found to improve the quality of life and Karnofsky's performance score in tumor patients [6] and relieve chemotherapy-induced phlebitis, radiation-induced stomatitis, and endocrinotherapy-induced menopause-like syndrome [17, 24, 25].

XH has been comprehensively used in tumor treatments, both to improve efficacy and reduce side effects of conventional therapies. XH was also reported to have effects on esophageal cancer and brain glioma [22, 23]. The clinical uses of XH are listed in Table 1.

Table 1: Clinical applications of XH on tumor therapies.

Diseases	Research method	Combined with/single use	Antitumor effect	Symptoms remission	Ref.
Non-Hodgkin lymphoma	RCT (60 cases)*	CHOP regimen	Enhance OS for 3 years	Relieve cancer-related symptoms Enhance KPS	[6]
Breast cancer	(60 cases) RCT (84 cases) (40 cases) (120 cases)	CEF regimen TEC regimen Letrozole Zoledronic acid	Enhance OS for 2 years Enhance RR Enhance FPS Treat bone metastasis	Relieve cancer-related symptoms Relieve endocrinotherapy-induced side-effects Relieve CIBP Enhance KPS Regulate immunity	[14–17]
Primary liver cancer	RCT (80 cases) Clinical observation (23 cases) Clinical observation (28 cases)	TAC (cisplatin) Single use Single use	Enhance RR Enhance OS for 1 year and 2 years	Enhance KPS Relieve cancer-related symptoms	[18–20]
Gastric cancer	RCT (80 cases) Clinical observation (48 cases)** Case report (2 cases)**	DCF regimen Single use Single use	Enhance RR	Relive chemotherapy-induced side-effects Regulate immunity	[21]
Esophageal cancer	RCT (18 cases)	Platinum and fluorouracil based regimens	Could not enhance the effects of chemotherapies	Improve the live quality Relieve cancer and chemotherapy-induced symptoms	[22]
Brain glioma	Case report (1 case)	TCM decoctions	Prolong the survival time to 3 years without undergoing resection Improve the live quality		[23]
Oral mucositis	RCT (60 cases)	Chinese patent medicine	Treat radiation-induced oral mucositis		[24]
Phlebitis	Case report (1 case)	Single use	Treat chemotherapy-induced phlebitis		[25]

*The cases number includes the total quantity in the randomized controlled trial (RCT).
**Unpublished observations.

4. XH Inhibits Tumor Cells via Multiple Pathways

4.1. XH Inhibits the Growth of Tumor Cells. Resisting cell death is the hallmark of cancer [53] and results in tumor growth. Tumor cells use several pathways to suppress apoptosis and acquire resistance to apoptotic agents, such as via expression of antiapoptotic proteins like Bcl-2 [54]. In fact, overexpression of Bcl-2 is a characteristic of drug-resistant tumor cells [55]. Drugs and microRNAs may regulate the Bcl-2 mediated apoptotic resistance [56, 57].

XH could induce H22 cell (mouse liver cancer cell line) and Bel-7402 cell (human liver cancer cell line) apoptosis by downregulating Bcl-2 expression in tumor-bearing mice [58, 59]. XH extract also inhibited the proliferation of human tumor cell lines MDA-MB-231 (breast cancer cell line), SMMC7721 (liver cancer cell line), T24 (bladder cancer cell line), A549 (lung cancer cell line), and LoVo (colorectal cancer cell line) *in vitro* [60, 61]. Therefore, XH inhibited tumor growth both *in vivo* and *in vitro*.

4.2. XH Prevents Invasion and Metastasis of Tumor Cells. Tumor cells invade adjacent tissues, which makes it difficult to be completely resected and liable to form metastasis. In the tumor microenvironment, tumor cells downregulate E-cadherin expression and overexpress N-cadherin and vimentin, which weakens intercellular adhesive attractions and facilitates invasion and metastasis. This process is called the epithelial-mesenchymal transition process [62] and could be inhibited by some TCMs [63]. Tumor cells degrade and remodel the extracellular matrix (ECM) by excessively secreting matrix metalloproteinases (MMPs) such as MMP-2 and MMP-9 [64].

XH can inhibit the epithelial-mesenchymal transition and ECM degradation. XH promoted mRNA levels of E-cadherin and suppressed N-cadherin expression in LoVo cells by regulating the ZEB1-SCRIB loop [61]. Additionally, XH had a potent effect on reducing the expressions of MMP-2 and MMP-9 in LoVo cells and 4T1 (mouse breast cancer) tumor-bearing mice [65, 66]. Therefore, XH intervention suppressed the invasion, migration, and metastasis of LoVo cells.

4.3. XH Inhibits Angiogenesis. Dysregulated angiogenesis can result in angiogenic diseases and is responsible for solid tumor growth and metastasis. When tumor tissues become hypoxic or hindered by the lack of nutrition, proangiogenic factors, such as vascular endothelial growth factor (VEGF) and nestin, predominate and result in angiogenesis and tumor progression [67, 68]. Bevacizumab or other angiogenesis-targeting drugs could improve the outcome in patients with metastatic cancer [69, 70]. The methanol extract of XH had an antiangiogenic effect on the zebrafish embryo [71] and XH could prevent the expression of VEGF *in vivo* [66].

4.4. XH Prevents the Proliferation of Cancer Stem Cells (CSCs). Since their initial discovery, CSCs have become a formidable challenge to cancer eradication [72]. CSCs can self-renew, give rise to cells that are different from them, and use common signaling pathways. CSCs may be responsible for the resistance of chemotherapeutic agents used to treat malignant tumors and may be the source of cells that give rise to distant metastases [73]. Plant-derived bioactive compounds can play a role in the regulation of CSC self-renewal [74]. XH could regulate and inhibit the growth of LAC (human lung cancer cell line) CSCs *in vivo* and *in vitro* by regulating the Wnt pathway [75].

4.5. XH Regulates the Tumor Immune Microenvironment (TIM). The TIM is complex and composed of immune cells that penetrate the tumor site via blood vessels and lymphoid capillaries [76]. TIM has an immunosuppressive role that involves synergistic suppressive cells, including regulatory T cells, tumor-associated macrophages, dendritic cells, and myeloid-derived suppressor cells (MDSCs) [77]. TIM also expresses immunosuppressive factors (IL-10, TGF-β), VEGF, and MMPs to prevent tumors detected from the antitumor immune cells and promote the invasion and metastasis of tumors [78].

Cancer immunotherapies targeting TIM have been developed and used in clinic [79], and TCM has effects on TIM by improving antitumor immunity and reversing immunosuppression [77]. One study found that XH ameliorated immunosuppression and inhibited tumor growth in tumor-bearing mice by reducing the expression of MDSCs [66]. Moreover, the chloroform, ethanol, and volatile oil extracts of XH could enhance the expression of immune system promoting factors (IL-2 and IFN-γ) and CD80 on antigen-presenting cells, decrease inhibiting factors (IL-10), and regulate the ratio of T-lymphocytes in a Walker256 (rat breast cancer cell line) tumor-bearing rat model [80–82].

5. Antitumor Effects and Pharmacological Studies of Phytochemicals in XH

5.1. Olibanum. Olibanum, commonly called frankincense, is the resin exuded from *Boswellia carteri* Birdw. and is used as an incense in religious and cultural ceremonies. Its medicinal properties are also widely recognized, mainly in the treatment of inflammatory conditions, some cancerous diseases, wound healing, and for its antimicrobial activity [83].

Olibanum contains triterpenoids, beta-boswellic acid, and its structurally related derivatives, which might be the most active compounds. Research showed that β-boswellic acid, 3-O-acetyl-β-boswellic acid, 11-keto-β-boswellic acid, and 3-O-acetyl-11-keto-β-boswellic acid inhibited DNA synthesis in HL-60 cells (human leukemia cells) [84]. Another study found that tirucallic acid, isolated from olibanum, is an effective Akt inhibitor and resulted in cytotoxic effects on human prostate cancer cells *in vivo* and *in vitro* [85]. β-boswellic acid could also inhibit NF-κB signaling, which is identified as an oncogenic factor [86].

5.2. Myrrh. Myrrh is the resin from *Commiphora myrrha* Engl. and has been used for centuries to treat internal tumors, obesity, liver disorders, malignant sores and ulcers, urinary complaints, intestinal worms, leucoderma, sinus problems, edema, and sudden paralytic seizures [87]. β-caryophyllene is an active component in the essential oils extracted from

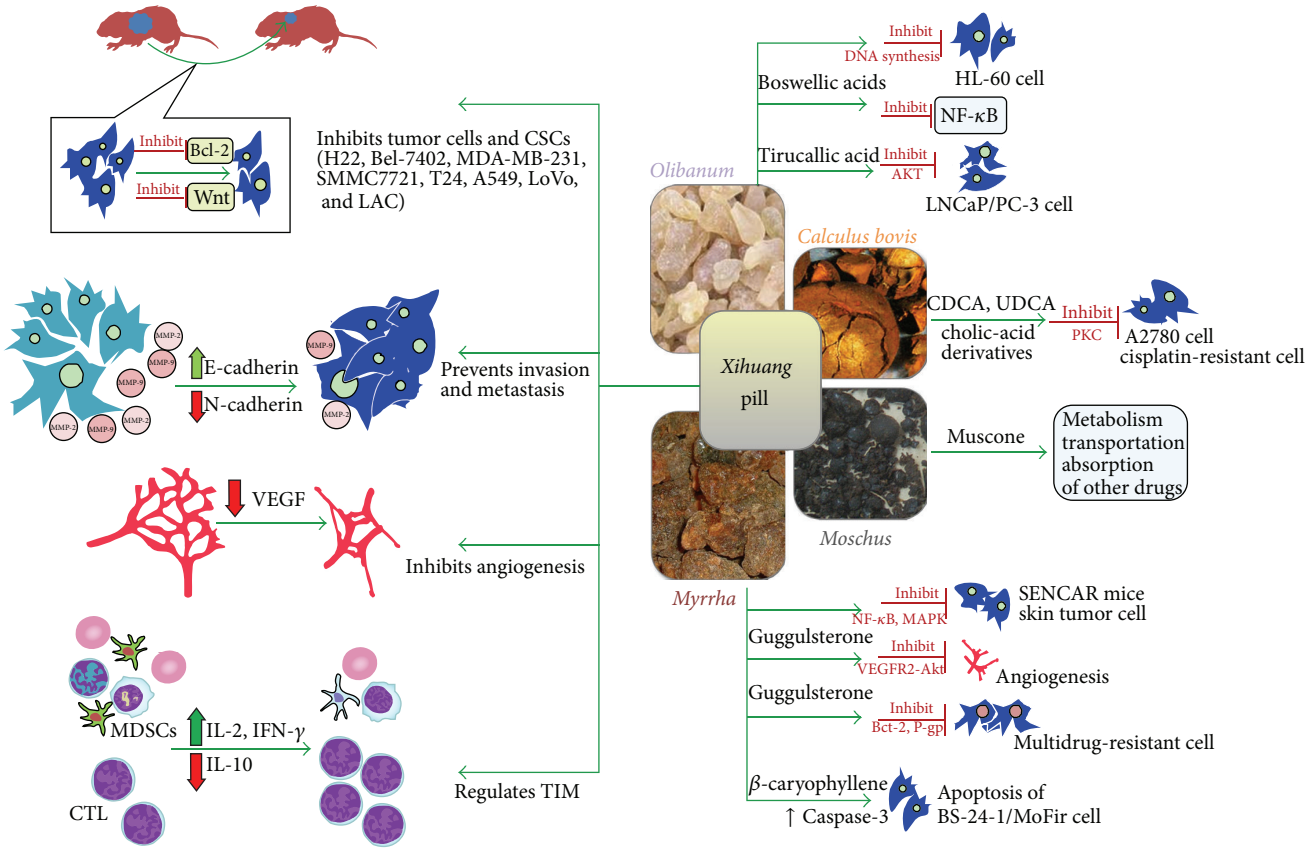

Figure 1: Effects and molecular mechanisms of *Xihuang* pill (XH) and its phytochemicals on tumor treatment. XH could prevent the progression and metastasis of tumors by inhibiting the growth, invasion, and angiogenesis of tumor cells and cancer stem cells. XH can also enhance immunity and reverse the immune suppressive microenvironment (myeloid-derived suppressor cells). Some of the compounds found in XH can inhibit various tumor cells by acting on multiple targets and regulating the metabolism, transportation, or absorption of one another.

myrrh and was found to potently induce apoptosis of BS-24-1 cells (mouse lymphoma cell line) accompanied by the activation of caspase-3 in tumor cells [88].

Guggulsterone (GUG) was identified as another major active component of myrrh that has potent inhibitory effects on tumor cells and anti-inflammatory effects by targeting the farnesoid X receptor [89]. Sarfaraz et al. [90] showed that GUG possesses anti-skin tumor effects in SENCAR mice by modulating the MAPK and NF-κB pathways. Xiao and Singh [91] found that *Z*-guggulsterone (an isomer of GUG) inhibited angiogenesis by suppressing the VEGF-VEGFR2-Akt signaling axis. Furthermore, studies indicated that coadministration of GUG resulted in a significant increase in chemosensitivity of multidrug-resistant human breast cancer MCF-7/DOX cells to doxorubicin (DOX) *in vivo* and *in vitro* via Bcl-2 and P-glycoprotein expression inhibition [92].

5.3. Moschus. *Moschus*, an herbal material used in TCM, was found to induce cell cycle arrest in human cervical carcinoma HeLa cells when combined with *Toona sinensis* [93]. Muscone is one of the active compounds of *Moschus* and has actions on the neural system [94]. Though muscone has not been reported to have any effects on tumors, there are potential mechanisms for tumor therapy. Muscone could significantly enhance cell membrane fluidity and improve the effect of geniposide transport across the human nasal epithelial cell monolayer [95]. Therefore, we hypothesize that facilitating the metabolism and absorption of antitumor drugs might be a mechanism of muscone.

5.4. Calculus bovis. *Calculus bovis* has been used in TCM for thousands years to treat high fever, convulsion, inflammation, and tumor. *Calculus bovis* contains bilirubin, bile acids, amino acids, and other compounds. For animal ethics reasons, *Calculus bovis* is identified by its components and artificially synthesized for medical use [96]. Research showed that chenodeoxycholic acid and ursodeoxycholic acid, two bile acids, had significant cytotoxic activity in ovarian cancer cells via induction of apoptosis and reduction of PKC activity [97]. Some new cholic-acid derivatives were synthesized and displayed a distinct cytotoxicity to tumor cell lines [98] (Figure 1).

6. Translation and Development of XH

6.1. Active Extraction from XH. Phytochemicals have been shown to have effects on tumors [99]. Chemotherapeutic

drugs, such as paclitaxel, are extracted and developed from natural compounds [100]. The antitumor effects of monomeric chemicals extracted from XH [84, 92] and their derivatives might be more effective [98]. With further in-depth study and synthetic modifications, we may discover new drugs for tumor treatment.

6.2. Research and Development (R&D) Based on Postmetabolic Products of XH. Serum pharmacology is a common method of *in vitro* studies on TCM compound formulas [61], but the chemicals in TCM in serum are unstable and interfere with other factors. Therefore, serum pharmacology is not entirely accepted in TCM basic science.

Extracts or single compounds from TCM contain identifiable compounds, but the compounds have not been metabolized and may have different biological function compared with those in serum [101]. For example, ginsenoside Rb1 has a minimal role in tumor prevention, but ginsenoside 20(S)-protopanaxadiol-aglycone, a metabolite of Rb1, significantly inhibited castration-resistant prostate cancer progression [102]. This might explain why effective clinical TCM compounds can fail in some *in vitro* experiments.

Chinese patent medicines can occasionally attain satisfactory clinical effects on tumors [103] and are becoming increasingly accepted by patients [104]. Further R&D into serum or gastrointestinal postmetabolic products is required, because these compounds could be responsible for the real actions of a TCM. For example, acetyl-11-keto-β-boswellic acid (AKBA), one of the most active compounds of olibanum, has numerous metabolites *in vivo* [105] that may affect different targets and cooperate or antagonize one another. Therefore, XH could be more effective if certain active metabolites were selected and others excluded.

6.3. High-Level Clinical Evidence for XH Is Necessary. TCM has a recorded history of over 2,000 years that may be used to guide modern treatments for disease and identify neglected but potentially useful treatment strategies [106]. However this process is often based on ancient TCM theories of tradition and history that fail to take into account evidence-based medicine. An increasing number of clinical trials investigating a variety of TCM interventions have been registered in international trial registries, and the design of registered TCM trials has improved by using techniques such as sample size estimation, blinding, and placebos [107]. XH has been shown to have effects on tumors in RCTs and small clinical observations (Table 1). However, more standardized studies should be registered and carried out.

7. Conclusion

TCM is based on a set of theories and regards Zheng (syndrome) as the core of a disease [108]. XH is effective for certain syndromes according to TCM and has been shown to have a significant effect on tumors. As a multicompound medicine, XH has multiple targets in tumor treatment and it is needed to farther study how these compounds and their metabolites work together and whether they have synergistic effects with each other. When combined with the conventional medicine XH could be very effective, and XH deserves additional attention in the antitumor research field.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Research Article

Clinical Effects of Xihuang Pill Combined with Chemotherapy in Patients with Advanced Colorectal Cancer

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Objective. To investigate the therapeutic effects of Xihuang pill combined with chemotherapy on advanced colorectal cancer. *Methods*. Sixty-three patients with advanced colorectal cancer were divided into an experimental group ($n = 32$) and control group ($n = 31$). Patients in the experimental group were treated with traditional Chinese medicine combined with Western medicine (i.e., Xihuang pill with FOLFOX or FOLFIRI chemotherapy), and those in the control group were treated with FOLFOX or FOLFIRI chemotherapy alone. Changes in therapeutic efficacy, side effects, blood coagulation function, and quality of life (QOL) were compared between the two groups. *Results*. The response rate was higher in the experimental than control group ($P = 0.011$). The QOL score in the experimental group was significantly lower after treatment than before treatment ($P = 0.003$), while no significant change was found in the control group. In the experimental group, the posttreatment activated partial thromboplastin time and prothrombin time after treatment were 30.05 ± 3.85 and 10.40 ± 1.25 s, respectively, which were prolonged compared with those before treatment (29.12 ± 4.03 and 9.85 ± 1.00 s; $P = 0.010$ and 0.021, respectively). *Conclusion*. In patients with advanced colorectal cancer, Xihuang pill combined with chemotherapy can significantly enhance the therapeutic effects compared with chemotherapy alone and improve patients' QOL and hypercoagulability.

1. Introduction

Colorectal cancer (CRC) is one of the most common tumors worldwide. According to epidemiological statistics, both the incidence and mortality rate of CRC ranked third among all malignant tumors in the United States in 2015 [1]. CRC is diagnosed at an advanced stage in most patients because of its occult symptoms, and the best opportunity for surgical treatment is thus lost. Although FOLFOX and FOFIRI chemotherapy are the international standards for the treatment of advanced CRC, the effect of chemotherapy is poor in most of these patients because of the high tumor load and low sensitivity to treatment as well as the patients' poor quality of life (QOL), intolerance to high-intensity chemotherapy, and hypercoagulable state with resultant predisposition to thromboembolic disease. Therefore, an understanding of the antitumor effects of traditional Chinese medicine is of great clinical significance. Xihuang pill, a classic anticancer Chinese medicine, contains four rare Chinese herbs: bezoar, musk, frankincense, and myrrh. This study was designed to investigate the effects of Xihuang pill combined with chemotherapy on the treatment efficacy, QOL improvement, and incidence of acute thrombosis in patients with advanced CRC.

2. Materials and Methods

2.1. Clinical Data. This study included 63 patients (34 male, 29 female) with advanced metastatic CRC admitted to the Oncology Department of Beijing Chaoyang Hospital from January 2013 to January 2016. The numbers of patients with pulmonary metastasis, liver metastasis, abdominal cavity and retroperitoneal lymph node metastasis, and peritoneal implantation metastasis were 24, 37, 41, and 28, respectively. The patients' ages ranged from 29 to 72 years (Table 1). All patients' diagnoses were confirmed by pathological examination, and none had a history of other tumors.

2.2. Inclusion and Exclusion Criteria. The inclusion criteria were as follows:

(i) Pathological diagnosis of CRC.

Table 1: General situation.

	Experimental group	Control group	P
Gender			0.712
Male	18 (52.9)	16 (47.1)	
Female	14 (48.3)	15 (51.7)	
Age (year)	58.13 ± 10.50	58.45 ± 10.01	0.900
ECOG	1.09 ± 0.73	1.06 ± 0.77	0.878

(ii) Treatment-naïvety with no history of radiotherapy, chemotherapy, or any type of antitumor therapy (for patients who developed relapse after adjuvant chemotherapy following radical resection, the last chemotherapy was completed within 6 months).

(iii) Eastern Cooperative Oncology Group (ECOG) physical status of ≤2 (Table 2).

(iv) Expected survival time of ≥3 months.

(v) Age of 20 to 79 years.

(vi) Measurable lesions (ability to measure at least one diameter line) identifiable by imaging or physical examination; maximum lesion diameter of ≥2 cm under conventional detection conditions or ≥1 cm by computed tomography (CT).

(vii) Neutrophilic granulocyte count of $\geq 1.5 \times 10^9$/L, platelet count of 80×10^9/L, hemoglobin concentration of ≥80 g/L, serum bilirubin concentration of ≤1.5 times the upper limit of normal, and alanine aminotransferase/aspartate aminotransferase concentrations of ≤2.5 times the upper limit of normal (≤5.0 times for patients with liver metastasis).

The exclusion criteria were as follows:

(i) Under treatment with other chemotherapies or radiotherapies.

(ii) Pregnancy, lactation.

(iii) Severe liver and renal impairment.

(iv) History of an uncontrollable mental disorder.

(v) Severe acute cardiac and cerebral vascular diseases.

2.3. Experimental Methods. Using a completely random grouping method, the patients were divided into an experimental group ($n = 32$) and a control group ($n = 31$). There were no significant differences in sex, age, or ECOG physical status between the two groups. Patients in the control group were treated with chemotherapy alone using either FOLFOX (LOHP at 85 mg/m^2 on day 1 + CF at 200 mg/m^2 on days 1 and 2 + 5-FU at 400 mg/m^2 on days 1 and 2 + 5-FU at 1200 mg/m^2 in a continuous intravenous infusion for 44 h every 14 days) or FOLFIRI (CPT-11 at 180 mg/m^2 on day 1 + CF at 200 mg/m^2 on days 1 and 2 + 5-FU at 400 mg/m^2 on days 1 and 2 + 5-FU at 1200 mg/m^2 in a continuous intravenous infusion for 44 h every 14 days). Patients in the experimental group were treated with one of the above chemotherapy regimens plus oral Xihuang pill (3 g/bottle; Beijing Tongrentang Group Co., Ltd.) administered at 3 g twice a day. In both groups, treatment efficacy was determined after four cycles of chemotherapy (one course of treatment was 56 days).

2.4. Clinical Outcome Measures. The clinical outcome measures were as follows:

(i) Routine blood tests, biochemical tests for liver and kidney function, and blood coagulation function testing before and after four cycles of chemotherapy.

(ii) Imaging examinations, such as CT and magnetic resonance imaging, before and after four cycles of chemotherapy.

(iii) Evaluation of ECOG physical status and chemotherapy-related toxicity, such as bone marrow suppression and gastrointestinal reactions. Toxicity evaluation was performed with reference to the Common Terminology Criteria for Adverse Events.

2.5. Response Evaluation Criteria in Solid Tumors (RECIST) Evaluation Criteria (Table 3). The following RECIST criteria were assessed:

(i) Measurable lesions (presence of at least one lesion with a diameter that could be accurately measured; the longest diameter was measured)

Tumorous Lesions

(a) Longest diameter of ≥10 mm by vernier caliper during clinical examination

(b) Longest diameter of ≥20 mm on chest radiograph and ≥10 mm on spiral CT (thinner scan is used if ≤5 mm on spiral CT)

Malignant Lymph Nodes

(a) Shortest lymph node diameter of ≥15 mm on spiral CT (thinner scan is used if ≤5 mm on spiral CT)

(ii) Target lesion selection

Selection of up to five measurable lesions, with up to two for each organ

(iii) Target lesion evaluation

2.6. Statistical Methods. Statistical analysis was performed using SPSS 13.0 software (SPSS Inc., Chicago, IL, USA). Measurement data are presented as mean ± standard deviation and enumeration data as frequency (rate). An independent-sample t-test was used for between-group comparisons, and a paired t-test was used for pre- and posttreatment intragroup comparisons. The data were not consistent with normality, and comparisons between groups were performed with the Mann–Whitney U test. The paired data were compared with the Wilcoxon signed rank test. A P value of <0.05 was considered statistically significant.

Table 2: Performance status by ECOG score standard (ZPS, 5 points).

Grade	Performance status
0	Fully active, able to carry on all predisease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, for example, light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities, up to and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Cannot carry on any self-care, totally confined to bed or chair
5	Dead

Table 3: Evaluation criteria of chemotherapy for solid tumors.

Response assessment	Evaluation criteria
CR	All target lesions have disappeared during the course of treatment and the pathological lymph nodes are reduced to <10 mm
PR	Decreases of at least 30% from base line have been noted in the sum of LD of target lesions
PD	There has been an increase of at least 20% in the sum of the LD of targeted lesions, and it is emphasized that the absolute value of the increased sum of LD is 5 mm, or new lesions appeared
SD	Between PD and PR

Table 4: Comparison of response rates.

Group	PR	SD	PD	RR (%)	*P* value
Experimental group	15	9	8	46.88	0.011
Control group	7	13	11	22.58	

3. Results

3.1. Therapeutic Efficacy. The response rate in the experimental group ($n = 32$) was 46.88% (complete response, $n = 0$; partial response, $n = 15$; stable disease, $n = 19$; progressive disease, $n = 8$). The response rate in the control group ($n = 31$) was 22.58% (complete response, $n = 0$; partial response, $n = 7$; stable disease, $n = 13$; progressive disease, $n = 11$). The difference in the response rates between the two groups was statistically significant (Table 4).

3.2. Tumor Markers. Before treatment, the carcinoembryonic antigen (CEA) concentration in the experimental and control groups was 66.5 and 68.0 ng/ml, respectively, with no significant difference. The CEA concentration was lower after treatment than before treatment in both the experimental and control groups (25.0 and 59.0 ng/ml, respectively); however, the difference was only statistically significant in the experimental group (Table 5).

3.3. Side Effects. No significant differences in side effects, including bone marrow suppression, gastrointestinal reactions, and abnormal liver and renal function, were found between the two groups ($P > 0.05$) (Table 6).

3.4. Coagulation Function. There were no statistically significant differences in the pretreatment activated partial thromboplastin time (APTT), prothrombin time (PT), or D-dimer concentration between the two groups (Table 7). In the experimental group, the APTT and PT were longer after treatment than before treatment, while the D-dimer concentration was lower. These differences were statistically significant. In the control group, however, no significant changes were observed in the APTT, PT, or D-dimer concentration before and after treatment (Table 8).

3.5. QOL. The pretreatment ECOG physical status in the control and experimental groups was 1.06 ± 0.77 and 1.09 ± 0.73, respectively ($P = 0.878$), without statistical significance. That after treatment was 1.16 ± 0.93 in the control group and 0.75 ± 0.57 in the experimental group. The ECOG physical status in the experimental group was significantly lower after treatment than before treatment, while in the control group, there was no significant change in the ECOG physical status before and after treatment (Table 9).

4. Discussion

Xihuang pill, a classic anticancer Chinese medicine, is composed of four rare Chinese herbs: bezoar, musk, frankincense, and myrrh. The combination of these four drugs powerfully clears away heat and toxic material and promotes blood circulation to remove blood stasis. These effects are made possible by the ability of bezoar to clear heat and detoxify, the ability of musk to activate blood stagnation and expel blood stasis, and the ability of frankincense and myrrh to promote blood and vital energy circulation and decrease swelling and pain. The four drugs are combined and made into pills with steamed rhubarb rice, which protects the physiological function of the stomach and eliminates pathogenic factors without injury. Xihuang pill alone or combined with other Western antitumor therapies is applied in the treatment of various malignant tumors and shows preferable antitumor effects on

Table 5: Comparison of CEA.

Groups	n	Pretreatment; ng/ml	Posttreatment; ng/ml	P
Experimental group	32	66.5 (27.3, 462.5)	25.0 (15.5, 117.5)	0.000
Control group	31	68.0 (25.0, 523.0)	59.0 (32.0, 410.0)	0.074
P		0.837	0.033	

Table 6: Side effects ($n = 63$).

Group	Bone marrow suppression	Gastrointestinal reaction	Abnormal liver function	Abnormal renal function
Experimental group	20	28	8	0
Control group	19	29	8	0
P value	0.674	1.000	0.941	—

Table 7: Coagulation function before treatment ($n = 63$).

Group	APTT (seconds)	PT (seconds)	D-dimer (mg/L)
Experimental group	29.12 ± 4.03	9.85 ± 1.00	1.26 ± 0.83
Control group	28.86 ± 3.93	9.61 ± 0.95	1.42 ± 1.39
P value	0.798	0.340	0.578

Table 8: Changes of coagulation function before and after treatment ($n = 63$).

Group		APTT (seconds)	PT (seconds)	D-dimer (mg/L)
Experimental group	Before treatment	29.12 ± 4.03	9.85 ± 1.00	1.26 ± 0.83
	After treatment	30.05 ± 3.85	10.40 ± 1.25	0.85 ± 0.44
	P value	0.010	0.021	0.010
Control group	Before treatment	28.86 ± 3.93	9.61 ± 0.95	1.42 ± 1.39
	After treatment	29.09 ± 3.71	9.75 ± 0.92	1.37 ± 1.20
	P value	0.053	0.155	0.625

Table 9: Changes of ECOG ($n = 63$).

Group	Time	ECOG	P value
Experimental group	Before treatment	1.09 ± 0.73	
	After treatment	0.75 ± 0.57	0.003
Control group	Before treatment	1.06 ± 0.77	
	After treatment	1.16 ± 0.93	0.5

breast cancer, lymphoma, esophageal cancer, ovarian cancer, and primary liver cancer [2–7].

Few clinical studies on the antitumor effects of Xihuang pill in the treatment of CRC have been reported to date. The present study has shown that Xihuang pill combined with chemotherapy (experimental group) has a significantly better response rate than chemotherapy alone (control group) when used as first-line treatment for advanced CRC, indicating that Xihuang pill is a promising adjuvant therapy that enhances the effectiveness of antitumor treatment. The concentration of CEA, a sensitive tumor marker of CRC, decreased in both groups after treatment; however, while the CEA concentration in the experimental group was significantly lower than that before treatment, there was no significant change in the control group. This further proves that Xihuang pill combined with chemotherapy provides better treatment control and reduces the tumor load further than does chemotherapy alone. Several possible reasons for this increased efficacy are as follows. First, Xihuang pill is a compounded Chinese medicine preparation that consists of four herbs: bezoar, musk, frankincense, and myrrh. Frankincense and myrrh contain a substantial amount of volatile oils, mainly a variety of alkenes, including β-, γ-, and δ-elemene. Alkenes exert an antitumor effect through their cytotoxic effects and enhance the immune function of the body [8, 9]. Detailed investigations of the antitumor mechanism of Xihuang pill have been performed in recent years. Duo et al. [10] established a subcutaneously transplanted human colon cancer model in nude mice and found that Xihuang pill inhibited the phosphorylation of extracellular signal-regulated protein kinases 1/2 (ERK1/2) and repressed the mitogen activated protein kinase signaling pathway, thereby inhibiting the proliferation of the human colon cancer xenografts and delaying tumor growth. These results demonstrate that Xihuang pill exerts an inhibitory effect on tumor cell proliferation. In addition, Xihuang pill regulates the expression of E and N cadherin through regulation of the ERK pathway and ZEB1-SCRIB cycle and represses the epithelial-mesenchymal transition of human colon cancer cells, thus inhibiting the invasion and metastasis of tumor cells [11].

In the present study, the ECOG performance status in the experimental group was significantly higher after treatment than before treatment, and the difference was statistically significant. This suggests that Xihuang pill combined with chemotherapy can significantly improve patients' QOL and increase the survival benefit. The main mechanism may involve the potent antitumor effect of Xihuang pill. Patients' QOL may be improved when their tumors are under control and symptoms are relieved. Additionally, Xihuang pill may also improve QOL of patients with advanced cancer by enhancing the body's immune function. Our study findings demonstrate that Xihuang pill plays a regulatory role in the tumor mass and immune microenvironment. In a previous study, ethanol extract of Xihuang pill increased the expression of interleukin-2 and interferon-γ, decreased the expression of interleukin-10, and regulated the ratios of CD3+, CD4+, and CD8+ T lymphocytes in the peripheral blood of rats with tumors [12]. Lan and Peng [13] included Xihuang pill combined with other antitumor therapy in the treatment of postoperative patients with CRC and patients with nasopharyngeal carcinoma undergoing chemotherapy, with an average observation time of 2 years and 7 months. The results showed that long-term use of Xihuang pill after conventional antitumor therapies helps to improve symptoms and prevent the recurrence and metastasis of tumors.

Approximately 90% of patients with malignant tumors are reportedly in a state of hypercoagulability. The application of traditional Chinese medicine that promotes blood circulation to remove blood stasis may improve this hypercoagulability and relieve or prevent its associated adverse events, therefore enhancing patients' QOL. In this study, the effect of Xihuang pill on blood coagulation function was also explored; in the experimental group, the APTT and PT were higher and the D-dimer concentration was lower after treatment than before treatment. The differences were of statistical significance. Therefore, this study has demonstrated that Xihuang pill has a significant curative effect on the hypercoagulative state of patients with CRC. Liu et al. [14] evaluated a subgroup of 80 patients with malignant tumors and found that application of Xihuang pill could safely improve the blood hypercoagulative state and reduce the platelet count and aggregation rate. According to the basic treatment principles of malignant tumors documented in traditional Chinese medicine literature (i.e., reducing phlegm and resolving masses, promoting blood circulation and detoxification, promoting the body's resistance, eliminating pathogenic factors, and purging and tonifying in combination [15]), Xihuang pill can improve patients' hypercoagulative state by its therapeutic effects of heat-clearing and detoxification, activating blood circulation and removing blood stasis, decreasing swelling, and relieving pain.

In summary, the results of this study show that Xihuang pill may improve the response rate, inhibit tumor growth, enhance the QOL, and reverse the hypercoagulative state in patients with CRC.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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[8] Y.-Y. Cai, Y.-Y. Xia, Y. Gu, C.-X. Liu, and D.-Y. Si, "Analysis on in vivo metabolic pathways of 3-acetyl-11-keto-β-boswellic acid in rats," *Chinese Traditional and Herbal Drugs*, vol. 44, no. 17, pp. 2427–2432, 2013.

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Laboratory Case Study—The Tumor Microenvironment-The Cancer Terrain
Stage 4 Colorectal Cancer with Liver Metastasis
Caucasian Male

Red Flags
Low Albumin. 1.1 (normal 1.2-2.2).
Early sarcopenia and cachexia and altered protein metabolism

Elevated Liver Function Tests
Alk Phos 242 H (39-117). ALT 62 (0-44)

Low Serum Iron 33 Low. (38-169)
Low Iron Saturation 11% Low (15-55)

C677T Single DNA MTHFR Mutation

Transforming Growth Factor beta1 7007 High (867-6662)

CEA 7.5 H (0-4.7)

CA 19-9 1223 H (0-35)

hs-CRP 84.02 (0-3.0)

Interleukin-6 13.2 H (0-12.2)

GGT 210 H (0-65)

Ceruloplasmin 41.8 H (16.0-31.0)

Copper (high normal) 159 (72-166)

Zinc 92 normal (56-134). Low Zinc to Copper Ratio. 1:1 or 2:1 is protective

Fibrinogen activity 483 (high normal) 193-507.

Neutrophil: Lymphocyte Ratio 57:19 3.0

Low Creatinine 0.56 (0.76-1.27)

Elevated CRP: Albumin Ratio. 84.2. : 3.9 21.6. (> 3.04 poor prognosis)

Low Albumin: Globulin Ratio. 1.1 (improved survival >1.29)

CASE study

LabCorp **Patient Report**

Patient: [redacted]
DOB: [redacted] Patient ID:

Control ID: 60008109142

Specimen ID: 016-494-0132-0
Date collected: 01/16/2018 1030 Local

TESTS	RESULT	FLAG	UNITS	REFERENCE INTERVAL	LAB
eGFR If NonAfricn Am	128		mL/min/1.73	>59	
eGFR If Africn Am	149		mL/min/1.73	>59	
BUN/Creatinine Ratio	18			9 - 20	
Sodium, Serum	141		mmol/L	134 - 144	01
Potassium, Serum	4.4		mmol/L	3.5 - 5.2	01
Chloride, Serum	98		mmol/L	96 - 106	01
Carbon Dioxide, Total	26		mmol/L	18 - 29	01
Calcium, Serum	9.5		mg/dL	8.7 - 10.2	01
Protein, Total, Serum	7.6		g/dL	6.0 - 8.5	01
Albumin, Serum	3.9		g/dL	3.5 - 5.5	01
Globulin, Total	3.7		g/dL	1.5 - 4.5	
A/G Ratio	**1.1**	**Low**		1.2 - 2.2	
Bilirubin, Total	0.4		mg/dL	0.0 - 1.2	01
Alkaline Phosphatase, S	**242**	**High**	IU/L	39 - 117	01
AST (SGOT)	30		IU/L	0 - 40	01
ALT (SGPT)	**62**	**High**	IU/L	0 - 44	01
Urinalysis, Complete					
Urinalysis Gross Exam					01
Specific Gravity	1.024			1.005 - 1.030	01
pH	6.5			5.0 - 7.5	01
Urine-Color	Yellow			Yellow	01
Appearance	Clear			Clear	01
WBC Esterase	Negative			Negative	01
Protein	Trace			Negative/Trace	01
Glucose	Negative			Negative	01
Ketones	Negative			Negative	01
Occult Blood	Negative			Negative	01
Bilirubin	Negative			Negative	01
Urobilinogen,Semi-Qn	0.2		mg/dL	0.2 - 1.0	01
Nitrite, Urine	Negative			Negative	01
Microscopic Examination					
Microscopic follows if indicated.					01
Microscopic Examination					
	See below:				01
WBC	0-5		/hpf	0 - 5	01
RBC	0-2		/hpf	0 - 2	01
Epithelial Cells (non renal)					
	None seen		/hpf	0 - 10	01
Casts	**Present**	**Abnormal**	/lpf	None seen	01
Cast Type	Hyaline casts			N/A	01
Mucus Threads	Present			Not Estab.	01
Bacteria	Few			None seen/Few	01

Yaatz 9240

LabCorp

Patient Report

Specimen ID: 016-494-0132-0
Control ID: 60008109142

Acct #: [redacted] **Phone:** (310) 453-5700 **Rte:** 00

[redacted]

Nalini Chilkov AC
2428 Santa Monica Blvd Ste 100
SANTA MONICA CA 90404

Patient Details
[redacted]
Gender: M **SSN:**
Patient ID:

Specimen Details
Date collected: 01/16/2018 1030 Local
Date received: 01/16/2018
Date entered: 01/16/2018
Date reported: 01/22/2018 1008 ET

Physician Details
Ordering: J CHILKOV
Referring:
ID:
NPI: 1215990767

General Comments & Additional Information
Total Volume: Not Provided **Fasting:** Yes

Ordered Items
CBC/Diff Ambiguous Default; Comp. Metabolic Panel (14); Urinalysis, Complete; Thyroid Panel With TSH; Iron and TIBC; G-6-PD, Quant, Blood and Hgb; Vitamin D, 1,25 + 25-Hydroxy; MTHFR; Trans. Growth Fact. beta 1*; Hemoglobin A1c; Thyroxine (T4) Free, Direct, S; Folate (Folic Acid), Serum; CEA; CA 19-9; Galectin-3; IGF-1; D-Dimer; Platelet Count on Citrated Bld; C-Reactive Protein, Cardiac; Interleukin-6, Plasma; Homocyst(e)ine, Plasma; LDH; GGT; Vitamin B12; Ceruloplasmin; Copper, Serum; Fibrinogen Activity; Zinc, Plasma or Serum; Insulin; Ferritin, Serum; Triiodothyronine,Free,Serum; Magnesium, RBC; Selenium, Serum/Plasma; Ambig Abbrev CMP14 Default; Venipuncture; Non LCA Req

TESTS	RESULT	FLAG	UNITS	REFERENCE INTERVAL	LAB
CBC/Diff Ambiguous Default					
WBC	8.3		x10E3/uL	3.4 - 10.8	01
RBC	4.86		x10E6/uL	4.14 - 5.80	01
Hemoglobin	**12.8**	**Low**	g/dL	13.0 - 17.7	01
Hematocrit	40.3		%	37.5 - 51.0	01
MCV	83		fL	79 - 97	01
MCH	**26.3**	**Low**	pg	26.6 - 33.0	01
MCHC	31.8		g/dL	31.5 - 35.7	01
RDW	12.9		%	12.3 - 15.4	01
Platelets	315		x10E3/uL	150 - 379	01
Neutrophils	57		%	Not Estab.	01
Lymphs	19		%	Not Estab.	01
Monocytes	10		%	Not Estab.	01
Eos	13		%	Not Estab.	01
Basos	1		%	Not Estab.	01
Neutrophils (Absolute)	4.7		x10E3/uL	1.4 - 7.0	01
Lymphs (Absolute)	1.6		x10E3/uL	0.7 - 3.1	01
Monocytes(Absolute)	0.8		x10E3/uL	0.1 - 0.9	01
Eos (Absolute)	**1.1**	**High**	x10E3/uL	0.0 - 0.4	01
Baso (Absolute)	0.1		x10E3/uL	0.0 - 0.2	01
Immature Granulocytes	0		%	Not Estab.	01
Immature Grans (Abs)	0.0		x10E3/uL	0.0 - 0.1	01
Comp. Metabolic Panel (14)					
Glucose, Serum	86		mg/dL	65 - 99	01
BUN	10		mg/dL	6 - 24	01
Creatinine, Serum	**0.56**	**Low**	mg/dL	0.76 - 1.27	01

Patient: [redacted] Patient ID:
DOB [redacted]
Control ID: 60008109142
Specimen ID: 016-494-0132-0
Date collected: 01/16/2018 1030 Local

TESTS	RESULT	FLAG	UNITS	REFERENCE INTERVAL	LAB
Thyroid Panel With TSH					
TSH	2.070		uIU/mL	0.450 - 4.500	01
Thyroxine (T4)	9.1		ug/dL	4.5 - 12.0	01
T3 Uptake	28		%	24 - 39	01
Free Thyroxine Index	2.5			1.2 - 4.9	
Iron and TIBC					
Iron Bind.Cap.(TIBC)	310		ug/dL	250 - 450	
UIBC	277		ug/dL	111 - 343	01
Iron, Serum	**33**	**Low**	ug/dL	38 - 169	01
Iron Saturation	**11**	**Low**	%	15 - 55	
G-6-PD, Quant, Blood and Hgb					
G-6-PD, Quant	10.5		U/g Hb	4.6 - 13.5	
Comment:					02

When decreased, G-6-PD, Quant. values are associated with acute hemolytic anemia when deficient individuals are exposed to oxidative stress, such as with certain medications (e.g., primaquine), infection, or ingestion of fava beans.
Caution: In patients with acute hemolysis (e.g., abnormally low RBC values), testing for G-6-PD may be falsely normal because older erythrocytes with a higher enzyme deficiency have been hemolyzed. Young erythrocytes and reticulocytes have normal or near-normal enzyme activity. Normal values of G-6-PD may be measured for several weeks following a hemolytic event.

Vitamin D, 1,25 + 25-Hydroxy				
Calcitriol(1,25 di-OH Vit D)	52.9	pg/mL	19.9 - 79.3	02
Vitamin D, 25-Hydroxy	59.4	ng/mL	30.0 - 100.0	01

Vitamin D deficiency has been defined by the Institute of Medicine and an Endocrine Society practice guideline as a level of serum 25-OH vitamin D less than 20 ng/mL (1,2). The Endocrine Society went on to further define vitamin D insufficiency as a level between 21 and 29 ng/mL (2).

1. IOM (Institute of Medicine). 2010. Dietary reference intakes for calcium and D. Washington DC: The National Academies Press.
2. Holick MF, Binkley NC, Bischoff-Ferrari HA, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. JCEM. 2011 Jul; 96(7):1911-30.

MTHFR

MTHFR, DNA Analysis 03

Result: C677T Single mutation (C677T) identified

Interpretation:
This patient's sample was analyzed for the MTHFR mutations C677T and A1298C. A single copy of the C677T mutation was

TESTS	RESULT	FLAG	UNITS	REFERENCE INTERVAL	LAB

identified. Results for the A1298C mutation were negative. The diagnosis of hyperhomocysteinemia can not rely on DNA testing alone but should take into consideration clinical findings and other studies, such as serum homocysteine levels. Because MTHFR mutations and their associated risks are inherited, genetic counseling is recommended.

Additional Information: 03

Methylenetetrahydrofolate reductase (MTHFR) is a key enzyme in the folate pathway and is responsible for the metabolism of homocysteine. There are two common variants in the MTHFR gene, c.655c>T (p.Ala222Vall), referred to as C677T, and c.1286A>C (p.Glu429Ala), referred to as A1298C. Individuals homozygous for C677T (two copies of the variant), have decreased activity of the MTHFR enzyme and a predisposition to hyperhomocysteinemia, particularly when deficient in folate. Hyperhomocysteinemia is a risk factor for venous thrombosis and coronary artery disease and is associated with an increased risk of fetal open neural tube defects. The C677T variant does not independently increase risk of these conditions in the absence of hyperhomocysteinemia. The A1298C variant is not associated with elevated homocysteine levels unless a C677T variant is also present; however, the clinical significance of heterozygosity for both C677T and A1298C is controversial. Population data suggest that these two variants are not present on the same chromosome, but rare exceptions have been reported of triple variant MTHFR genotypes (ie. homozygous for one variant and heterozygous for the other). Homozygosity for C677T has an estimated frequency of 10% to 15% in Caucasians and 25% in Hispanics.

Additional information:

Dietary folic acid, B6 and B12 supplementation has been suggested to lower homocysteine levels in some people. Folic acid supplementation has been shown to reduce the occurrence of neural tube defects. Genetic counselors are available for health care providers to discuss results at 1-800-345-GENE.

Methodology:

DNA analysis of the MTHFR gene was performed by PCR amplification followed by restriction analysis. The diagnostic sensitivity is >99% for both. Molecular-based testing is highly accurate, but as in any laboratory test, rare diagnostic errors may occur. All test results must be combined with clinical information for the most accurate interpretation.

This test was developed and its performance characteristics determined by LabCorp. It has not been cleared or approved by the Food and Drug Administration.

References:

Botto LD, Yang Q. Am J Epidemiol 2000; 151(9):862-877.
Eldibany MM, Caprini JA. Arch Pathol Lab Med 2007; 131(6):872-884.
Frosst P et al. Nat Genet 1995; 10(1):111-113.
Hickey SE et al. Genet Med 2013; 15(2):153-156.
Lockwood C et al. Obstet Gynecol 2011; 118(3):730-740.
Simone B et al. Eur J Epidemiol 2013; 28(8):621-647.

Chevonne Eversley, PhD, FACMG
Melissa A Hayden, PhD, FACMG

Patient: [redacted]
DOB: [redacted] Patient ID:

Control ID: 60008109142

Specimen ID: 016-494-0132-0
Date collected: 01/16/2018 1030 Local

TESTS	RESULT	FLAG	UNITS	REFERENCE INTERVAL	LAB
Suzette M Huguenin, PhD, FACMG Annette K Taylor, M.S., PhD, FACMG Alecia Willis, PhD, FACMG Hongli Zhan, PhD, FACMG Joseph B Kearney, PhD, FACMG					
Trans. Growth Fact. beta 1*	7007	High	pg/mL	867 - 6662	04
The result is reported in pg/mL. The assay range is approximately 98 to 400,000. The reference range for a healthy population is 867-6662. However it should be noted that these ranges are obtained from a limited population of apparently healthy adults and are not diagnostic thresholds. *This test was developed and its performance characteristics determined by Viracor Eurofins. It has not been cleared or approved by the U.S. Food and Drug Administration.					
Hemoglobin A1c					
Hemoglobin A1c	5.3		%	4.8 - 5.6	01
Please Note: Pre-diabetes: 5.7 - 6.4 Diabetes: >6.4 Glycemic control for adults with diabetes: <7.0					01
Thyroxine (T4) Free, Direct, S					
T4,Free(Direct)	1.42		ng/dL	0.82 - 1.77	01
Folate (Folic Acid), Serum					
Folate (Folic Acid), Serum	10.8		ng/mL	>3.0	01
Note: A serum folate concentration of less than 3.1 ng/mL is considered to represent clinical deficiency.					01
CEA **Roche ECLIA methodology**	7.5	High	ng/mL	0.0 - 4.7 **Nonsmokers <3.9** **Smokers <5.6**	01
CA 19-9 **Results confirmed on dilution.** **Roche ECLIA methodology**	1223	High	U/mL	0 - 35	01
Galectin-3	10.9		ng/mL	<22.2	02
Reference range of <22.2 ng/mL applies to population without known heart disease. Galectin-3 is NOT a marker of cardiac distress or decompensation. Galectin-3 is a marker of fibrosis and adverse remodeling resulting in a more progressive form of chronic heart					

TESTS	RESULT	FLAG	UNITS	REFERENCE INTERVAL	LAB

failure. The BGM Galectin-3 assay results should be interpreted in conjunction with clinical evaluation as an aid in assessing the prognosis of patients diagnosed with chronic heart failure.
* Galectin-3 levels less than or equal to 17.8 ng/mL - LOWER risk of adverse outcomes including mortality or hospitalization.
* Galectin-3 levels greater than 17.8 ng/mL - HIGHER risk of adverse outcomes including mortality or hospitalization.
* Galectin-3 levels between 17.8 ng/mL and 25.9 ng/mL should be interpreted with caution because these values lie within the reference range.
Additional Considerations
- Approximately 30% of NYHA class II/III outpatient population were found to have elevated galectin-3 levels (>17.8 ng/mL). [1]
- Elevated galectin-3 is found in similar percentages of patients with systolic dysfunction and preserved ejection fraction. [1]
- Galectin-3 shows modest correlations with clinical variables, including Age (slightly higher levels in older subjects), Gender (women have slightly higher values) certain co-morbidities (diabetes and atrial fibrillation), and NYHA classification. [2]
- Once elevated galectin-3 levels are generally stable over time. [2]
- Drugs effective in the management of patients with heart failure often fail to reduce levels of galectin-3 and galectin-3 levels should not be used to guide therapy.
* Galectin-3 testing was cleared by the FDA for use in patients with chronic heart failure only. [1]

(1) BG Galectin-3 Product Label
(2) de Boer, R; Lok, D; Jaarsma, T, et al. Value of Plasma Galectin-3 levels in Heart Failure with Reduced and Preserved Ejection Fraction. Ann Medicine, 2011; 43(1):60-68.

IGF-1					
Insulin-Like Growth Factor I	**245**	**High**	ng/mL	75 - 216	02
D-Dimer	**3.18**	**High**	mg/L FEU	0.00 - 0.49	01

According to the assay manufacturer's published package insert, a normal (<0.50 mg/L FEU) D-dimer result in conjunction with a non-high clinical probability assessment, excludes deep vein thrombosis (DVT) *and pulmonary* embolism (PE) with high sensitivity.
D-dimer values increase with age and this can make VTE exclusion of an older population difficult. To address this, the American College of Physicians, based on best available evidence and recent guidelines, recommends that clinicians use age-adjusted D-dimer thresholds in patients greater than 50 years of age with: a) a low probability of PE who do not meet all Pulmonary Embolism Rule Out Criteria, or b) in those with intermediate probability of PE. The formula for an

Patient: [redacted]
DOB: [redacted] Patient ID:

Control ID: 60008109142

Specimen ID: 016-494-0132-0
Date collected: 01/16/2018 1030 Local

TESTS	RESULT	FLAG	UNITS	REFERENCE INTERVAL	LAB
age-adjusted D-dimer cut-off is "age/100". For example, a 60 year old patient would have an age-adjusted cut-off of 0.60 mg/L FEU and an 80 year old 0.80 mg/L FEU.					
Platelet Count on Citrated Bld					
Plt Count, Citrated Bld	219		X10E3/uL	150 - 379	01
C-Reactive Protein, Cardiac	**84.02**	**High**	mg/L	0.00 - 3.00	01
Results confirmed on dilution.					
Relative Risk for Future Cardiovascular Event					
Low				<1.00	
Average				1.00 - 3.00	
High				>3.00	
Interleukin-6, Plasma	**13.2**	**High**	pg/mL	0.0 - 12.2	02
Results for this test are for research purposes only by the assay's manufacturer. The performance characteristics of this product have not been established. Results should not be used as a diagnostic procedure without confirmation of the diagnosis by another medically established diagnostic product or procedure.					
Homocyst(e)ine, Plasma	7.3		umol/L	0.0 - 15.0	01
LDH	222		IU/L	121 - 224	01
GGT	**210**	**High**	IU/L	0 - 65	01
Vitamin B12	759		pg/mL	232 - 1245	01
Ceruloplasmin	**41.8**	**High**	mg/dL	16.0 - 31.0	02
Copper, Serum	159		ug/dL	72 - 166	02
			Detection Limit = 5		
Fibrinogen Activity	483		mg/dL	193 - 507	01
Zinc, Plasma or Serum	92		ug/dL	56 - 134	02
			Detection Limit = 5		
Insulin	6.7		uIU/mL	2.6 - 24.9	01
Ferritin, Serum	213		ng/mL	30 - 400	01
Triiodothyronine,Free,Serum	3.2		pg/mL	2.0 - 4.4	01
Magnesium, RBC	6.0		mg/dL	4.2 - 6.8	02
Selenium, Serum/Plasma	146		ug/L	79 - 326	02

Patient: [redacted]
DOB: [redacted] Patient ID: Control ID: 60008109142

Specimen ID: 016-494-0132-0
Date collected: 01/16/2018 1030 Local

TESTS	RESULT	FLAG	UNITS	REFERENCE INTERVAL	LAB
				Detection Limit = 10	

Ambig Abbrev CMP14 Default 01

A hand-written panel/profile was received from your office. In accordance with the LabCorp Ambiguous Test Code Policy dated July 2003, we have completed your order by using the closest currently or formerly recognized AMA panel. We have assigned Comprehensive Metabolic Panel (14), Test Code #322000 to this request. If this is not the testing you wished to receive on this specimen, please contact the LabCorp Client Inquiry/Technical Services Department to clarify the test order. We appreciate your business.

01	SO	LabCorp San Diego 13112 Evening Creek Dr So Ste 200, San Diego, CA 92128-4108	Dir: Jenny Galloway, MD
02	BN	LabCorp Burlington 1447 York Court, Burlington, NC 27215-3361	Dir: William F Hancock, MD
03	UY	Esoterix Coagulation Lab 8490 Upland Drive Ste 100, Englewood, CO 80112-7116	Dir: Brian F. Poirier, MD
04	NEWXW	Viracor Eurofins 1001 NW Technology Drive, Lees Summit, MO 64086-5603	Dir: Michelle Altrich, PhD

For inquiries, the physician may contact **Branch: 800-859-6046 Lab: 858-668-3700**

CASE study

LabCorp **Patient Report**

Patient: [redacted]
DOB: [redacted] Patient ID:

Control ID: 60008109142

Specimen ID: 016-494-0132-0
Date collected: 01/16/2018 1030 Local

TESTS	RESULT	FLAG	UNITS	REFERENCE INTERVAL	LAB
eGFR If NonAfricn Am	128		mL/min/1.73	>59	
eGFR If Africn Am	149		mL/min/1.73	>59	
BUN/Creatinine Ratio	18			9 - 20	
Sodium, Serum	141		mmol/L	134 - 144	01
Potassium, Serum	4.4		mmol/L	3.5 - 5.2	01
Chloride, Serum	98		mmol/L	96 - 106	01
Carbon Dioxide, Total	26		mmol/L	18 - 29	01
Calcium, Serum	9.5		mg/dL	8.7 - 10.2	01
Protein, Total, Serum	7.6		g/dL	6.0 - 8.5	01
Albumin, Serum	3.9		g/dL	3.5 - 5.5	01
Globulin, Total	3.7		g/dL	1.5 - 4.5	
A/G Ratio	**1.1**	**Low**		1.2 - 2.2	
Bilirubin, Total	0.4		mg/dL	0.0 - 1.2	01
Alkaline Phosphatase, S	**242**	**High**	IU/L	39 - 117	01
AST (SGOT)	30		IU/L	0 - 40	01
ALT (SGPT)	**62**	**High**	IU/L	0 - 44	01
Urinalysis, Complete					
Urinalysis Gross Exam					01
Specific Gravity	1.024			1.005 - 1.030	01
pH	6.5			5.0 - 7.5	01
Urine-Color	Yellow			Yellow	01
Appearance	Clear			Clear	01
WBC Esterase	Negative			Negative	01
Protein	Trace			Negative/Trace	01
Glucose	Negative			Negative	01
Ketones	Negative			Negative	01
Occult Blood	Negative			Negative	01
Bilirubin	Negative			Negative	01
Urobilinogen,Semi-Qn	0.2		mg/dL	0.2 - 1.0	01
Nitrite, Urine	Negative			Negative	01
Microscopic Examination					
Microscopic follows if indicated.					01
Microscopic Examination					
	See below:				01
WBC	0-5		/hpf	0 - 5	01
RBC	0-2		/hpf	0 - 2	01
Epithelial Cells (non renal)					
	None seen		/hpf	0 - 10	01
Casts	**Present**	**Abnormal**	/lpf	None seen	01
Cast Type	Hyaline casts			N/A	01
Mucus Threads	Present			Not Estab.	01
Bacteria	Few			None seen/Few	01

Yaatz 9240

LabCorp

Patient Report

Specimen ID: 016-494-0132-0
Control ID: 60008109142

Acct #: [redacted] **Phone:** (310) 453-5700 **Rte:** 00

[redacted]

Nalini Chilkov AC
2428 Santa Monica Blvd Ste 100
SANTA MONICA CA 90404

Patient Details
[redacted]
Gender: M **SSN:**
Patient ID:

Specimen Details
Date collected: 01/16/2018 1030 Local
Date received: 01/16/2018
Date entered: 01/16/2018
Date reported: 01/22/2018 1008 ET

Physician Details
Ordering: J CHILKOV
Referring:
ID:
NPI: 1215990767

General Comments & Additional Information
Total Volume: Not Provided **Fasting:** Yes

Ordered Items
CBC/Diff Ambiguous Default; Comp. Metabolic Panel (14); Urinalysis, Complete; Thyroid Panel With TSH; Iron and TIBC; G-6-PD, Quant, Blood and Hgb; Vitamin D, 1,25 + 25-Hydroxy; MTHFR; Trans. Growth Fact. beta 1*; Hemoglobin A1c; Thyroxine (T4) Free, Direct, S; Folate (Folic Acid), Serum; CEA; CA 19-9; Galectin-3; IGF-1; D-Dimer; Platelet Count on Citrated Bld; C-Reactive Protein, Cardiac; Interleukin-6, Plasma; Homocyst(e)ine, Plasma; LDH; GGT; Vitamin B12; Ceruloplasmin; Copper, Serum; Fibrinogen Activity; Zinc, Plasma or Serum; Insulin; Ferritin, Serum; Triiodothyronine,Free,Serum; Magnesium, RBC; Selenium, Serum/Plasma; Ambig Abbrev CMP14 Default; Venipuncture; Non LCA Req

TESTS	RESULT	FLAG	UNITS	REFERENCE INTERVAL	LAB
CBC/Diff Ambiguous Default					
WBC	8.3		x10E3/uL	3.4 - 10.8	01
RBC	4.86		x10E6/uL	4.14 - 5.80	01
Hemoglobin	**12.8**	**Low**	g/dL	13.0 - 17.7	01
Hematocrit	40.3		%	37.5 - 51.0	01
MCV	83		fL	79 - 97	01
MCH	**26.3**	**Low**	pg	26.6 - 33.0	01
MCHC	31.8		g/dL	31.5 - 35.7	01
RDW	12.9		%	12.3 - 15.4	01
Platelets	315		x10E3/uL	150 - 379	01
Neutrophils	57		%	Not Estab.	01
Lymphs	19		%	Not Estab.	01
Monocytes	10		%	Not Estab.	01
Eos	13		%	Not Estab.	01
Basos	1		%	Not Estab.	01
Neutrophils (Absolute)	4.7		x10E3/uL	1.4 - 7.0	01
Lymphs (Absolute)	1.6		x10E3/uL	0.7 - 3.1	01
Monocytes(Absolute)	0.8		x10E3/uL	0.1 - 0.9	01
Eos (Absolute)	**1.1**	**High**	x10E3/uL	0.0 - 0.4	01
Baso (Absolute)	0.1		x10E3/uL	0.0 - 0.2	01
Immature Granulocytes	0		%	Not Estab.	01
Immature Grans (Abs)	0.0		x10E3/uL	0.0 - 0.1	01
Comp. Metabolic Panel (14)					
Glucose, Serum	86		mg/dL	65 - 99	01
BUN	10		mg/dL	6 - 24	01
Creatinine, Serum	**0.56**	**Low**	mg/dL	0.76 - 1.27	01

Patient: [redacted] Patient ID:
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TESTS	RESULT	FLAG	UNITS	REFERENCE INTERVAL	LAB
Thyroid Panel With TSH					
TSH	2.070		uIU/mL	0.450 - 4.500	01
Thyroxine (T4)	9.1		ug/dL	4.5 - 12.0	01
T3 Uptake	28		%	24 - 39	01
Free Thyroxine Index	2.5			1.2 - 4.9	
Iron and TIBC					
Iron Bind.Cap.(TIBC)	310		ug/dL	250 - 450	
UIBC	277		ug/dL	111 - 343	01
Iron, Serum	**33**	**Low**	ug/dL	38 - 169	01
Iron Saturation	**11**	**Low**	%	15 - 55	
G-6-PD, Quant, Blood and Hgb					
G-6-PD, Quant	10.5		U/g Hb	4.6 - 13.5	
Comment:					02

When decreased, G-6-PD, Quant. values are associated with acute hemolytic anemia when deficient individuals are exposed to oxidative stress, such as with certain medications (e.g., primaquine), infection, or ingestion of fava beans.
Caution: In patients with acute hemolysis (e.g., abnormally low RBC values), testing for G-6-PD may be falsely normal because older erythrocytes with a higher enzyme deficiency have been hemolyzed. Young erythrocytes and reticulocytes have normal or near-normal enzyme activity. Normal values of G-6-PD may be measured for several weeks following a hemolytic event.

Vitamin D, 1,25 + 25-Hydroxy				
Calcitriol(1,25 di-OH Vit D)	52.9	pg/mL	19.9 - 79.3	02
Vitamin D, 25-Hydroxy	59.4	ng/mL	30.0 - 100.0	01

Vitamin D deficiency has been defined by the Institute of Medicine and an Endocrine Society practice guideline as a level of serum 25-OH vitamin D less than 20 ng/mL (1,2). The Endocrine Society went on to further define vitamin D insufficiency as a level between 21 and 29 ng/mL (2).

1. IOM (Institute of Medicine). 2010. Dietary reference intakes for calcium and D. Washington DC: The National Academies Press.
2. Holick MF, Binkley NC, Bischoff-Ferrari HA, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. JCEM. 2011 Jul; 96(7):1911-30.

MTHFR

MTHFR, DNA Analysis 03

Result: C677T Single mutation (C677T) identified

Interpretation:
This patient's sample was analyzed for the MTHFR mutations C677T and A1298C. A single copy of the C677T mutation was

TESTS	RESULT	FLAG	UNITS	REFERENCE INTERVAL	LAB

identified. Results for the A1298C mutation were negative. The diagnosis of hyperhomocysteinemia can not rely on DNA testing alone but should take into consideration clinical findings and other studies, such as serum homocysteine levels. Because MTHFR mutations and their associated risks are inherited, genetic counseling is recommended.

Additional Information: 03

Methylenetetrahydrofolate reductase (MTHFR) is a key enzyme in the folate pathway and is responsible for the metabolism of homocysteine. There are two common variants in the MTHFR gene, c.655c>T (p.Ala222Vall), referred to as C677T, and c.1286A>C (p.Glu429Ala), referred to as A1298C. Individuals homozygous for C677T (two copies of the variant), have decreased activity of the MTHFR enzyme and a predisposition to hyperhomocysteinemia, particularly when deficient in folate. Hyperhomocysteinemia is a risk factor for venous thrombosis and coronary artery disease and is associated with an increased risk of fetal open neural tube defects. The C677T variant does not independently increase risk of these conditions in the absence of hyperhomocysteinemia. The A1298C variant is not associated with elevated homocysteine levels unless a C677T variant is also present; however, the clinical significance of heterozygosity for both C677T and A1298C is controversial. Population data suggest that these two variants are not present on the same chromosome, but rare exceptions have been reported of triple variant MTHFR genotypes (ie. homozygous for one variant and heterozygous for the other). Homozygosity for C677T has an estimated frequency of 10% to 15% in Caucasians and 25% in Hispanics.

Additional information:

Dietary folic acid, B6 and B12 supplementation has been suggested to lower homocysteine levels in some people. Folic acid supplementation has been shown to reduce the occurrence of neural tube defects. Genetic counselors are available for health care providers to discuss results at 1-800-345-GENE.

Methodology:

DNA analysis of the MTHFR gene was performed by PCR amplification followed by restriction analysis. The diagnostic sensitivity is >99% for both. Molecular-based testing is highly accurate, but as in any laboratory test, rare diagnostic errors may occur. All test results must be combined with clinical information for the most accurate interpretation.

This test was developed and its performance characteristics determined by LabCorp. It has not been cleared or approved by the Food and Drug Administration.

References:

Botto LD, Yang Q. Am J Epidemiol 2000; 151(9):862-877.
Eldibany MM, Caprini JA. Arch Pathol Lab Med 2007; 131(6):872-884.
Frosst P et al. Nat Genet 1995; 10(1):111-113.
Hickey SE et al. Genet Med 2013; 15(2):153-156.
Lockwood C et al. Obstet Gynecol 2011; 118(3):730-740.
Simone B et al. Eur J Epidemiol 2013; 28(8):621-647.

Chevonne Eversley, PhD, FACMG
Melissa A Hayden, PhD, FACMG

Patient: [redacted]
DOB: [redacted] Patient ID:

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TESTS	RESULT	FLAG	UNITS	REFERENCE INTERVAL	LAB
Suzette M Huguenin, PhD, FACMG Annette K Taylor, M.S., PhD, FACMG Alecia Willis, PhD, FACMG Hongli Zhan, PhD, FACMG Joseph B Kearney, PhD, FACMG					
Trans. Growth Fact. beta 1*	7007	High	pg/mL	867 - 6662	04
The result is reported in pg/mL. The assay range is approximately 98 to 400,000. The reference range for a healthy population is 867-6662. However it should be noted that these ranges are obtained from a limited population of apparently healthy adults and are not diagnostic thresholds. *This test was developed and its performance characteristics determined by Viracor Eurofins. It has not been cleared or approved by the U.S. Food and Drug Administration.					
Hemoglobin A1c					
Hemoglobin A1c	5.3		%	4.8 - 5.6	01
Please Note: Pre-diabetes: 5.7 - 6.4 Diabetes: >6.4 Glycemic control for adults with diabetes: <7.0					01
Thyroxine (T4) Free, Direct, S					
T4,Free(Direct)	1.42		ng/dL	0.82 - 1.77	01
Folate (Folic Acid), Serum					
Folate (Folic Acid), Serum	10.8		ng/mL	>3.0	01
Note: A serum folate concentration of less than 3.1 ng/mL is considered to represent clinical deficiency.					01
CEA **Roche ECLIA methodology**	7.5	High	ng/mL	0.0 - 4.7 **Nonsmokers <3.9** **Smokers <5.6**	01
CA 19-9 **Results confirmed on dilution.** **Roche ECLIA methodology**	1223	High	U/mL	0 - 35	01
Galectin-3	10.9		ng/mL	<22.2	02
Reference range of <22.2 ng/mL applies to population without known heart disease. Galectin-3 is NOT a marker of cardiac distress or decompensation. Galectin-3 is a marker of fibrosis and adverse remodeling resulting in a more progressive form of chronic heart					

TESTS	RESULT	FLAG	UNITS	REFERENCE INTERVAL	LAB

failure. The BGM Galectin-3 assay results should be interpreted in conjunction with clinical evaluation as an aid in assessing the prognosis of patients diagnosed with chronic heart failure.
* Galectin-3 levels less than or equal to 17.8 ng/mL - LOWER risk of adverse outcomes including mortality or hospitalization.
* Galectin-3 levels greater than 17.8 ng/mL - HIGHER risk of adverse outcomes including mortality or hospitalization.
* Galectin-3 levels between 17.8 ng/mL and 25.9 ng/mL should be interpreted with caution because these values lie within the reference range.
Additional Considerations
- Approximately 30% of NYHA class II/III outpatient population were found to have elevated galectin-3 levels (>17.8 ng/mL). [1]
- Elevated galectin-3 is found in similar percentages of patients with systolic dysfunction and preserved ejection fraction. [1]
- Galectin-3 shows modest correlations with clinical variables, including Age (slightly higher levels in older subjects), Gender (women have slightly higher values) certain co-morbidities (diabetes and atrial fibrillation), and NYHA classification. [2]
- Once elevated galectin-3 levels are generally stable over time. [2]
- Drugs effective in the management of patients with heart failure often fail to reduce levels of galectin-3 and galectin-3 levels should not be used to guide therapy.
* Galectin-3 testing was cleared by the FDA for use in patients with chronic heart failure only. [1]

(1) BG Galectin-3 Product Label
(2) de Boer, R; Lok, D; Jaarsma, T, et al. Value of Plasma Galectin-3 levels in Heart Failure with Reduced and Preserved Ejection Fraction. Ann Medicine, 2011; 43(1):60-68.

IGF-1					
Insulin-Like Growth Factor I	**245**	**High**	ng/mL	75 - 216	02
D-Dimer	**3.18**	**High**	mg/L FEU	0.00 - 0.49	01

According to the assay manufacturer's published package insert, a normal (<0.50 mg/L FEU) D-dimer result in conjunction with a non-high clinical probability assessment, excludes deep vein thrombosis (DVT) *and pulmonary* embolism (PE) with high sensitivity.
D-dimer values increase with age and this can make VTE exclusion of an older population difficult. To address this, the American College of Physicians, based on best available evidence and recent guidelines, recommends that clinicians use age-adjusted D-dimer thresholds in patients greater than 50 years of age with: a) a low probability of PE who do not meet all Pulmonary Embolism Rule Out Criteria, or b) in those with intermediate probability of PE. The formula for an

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age-adjusted D-dimer cut-off is "age/100". For example, a 60 year old patient would have an age-adjusted cut-off of 0.60 mg/L FEU and an 80 year old 0.80 mg/L FEU.					
Platelet Count on Citrated Bld					
Plt Count, Citrated Bld	219		X10E3/uL	150 - 379	01
C-Reactive Protein, Cardiac	**84.02**	**High**	mg/L	0.00 - 3.00	01
Results confirmed on dilution.					
Relative Risk for Future Cardiovascular Event					
Low				<1.00	
Average				1.00 - 3.00	
High				>3.00	
Interleukin-6, Plasma	**13.2**	**High**	pg/mL	0.0 - 12.2	02
Results for this test are for research purposes only by the assay's manufacturer. The performance characteristics of this product have not been established. Results should not be used as a diagnostic procedure without confirmation of the diagnosis by another medically established diagnostic product or procedure.					
Homocyst(e)ine, Plasma	7.3		umol/L	0.0 - 15.0	01
LDH	222		IU/L	121 - 224	01
GGT	**210**	**High**	IU/L	0 - 65	01
Vitamin B12	759		pg/mL	232 - 1245	01
Ceruloplasmin	**41.8**	**High**	mg/dL	16.0 - 31.0	02
Copper, Serum	159		ug/dL	72 - 166	02
			Detection Limit = 5		
Fibrinogen Activity	483		mg/dL	193 - 507	01
Zinc, Plasma or Serum	92		ug/dL	56 - 134	02
			Detection Limit = 5		
Insulin	6.7		uIU/mL	2.6 - 24.9	01
Ferritin, Serum	213		ng/mL	30 - 400	01
Triiodothyronine,Free,Serum	3.2		pg/mL	2.0 - 4.4	01
Magnesium, RBC	6.0		mg/dL	4.2 - 6.8	02
Selenium, Serum/Plasma	146		ug/L	79 - 326	02

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TESTS	RESULT	FLAG	UNITS	REFERENCE INTERVAL	LAB
				Detection Limit = 10	

Ambig Abbrev CMP14 Default 01

A hand-written panel/profile was received from your office. In accordance with the LabCorp Ambiguous Test Code Policy dated July 2003, we have completed your order by using the closest currently or formerly recognized AMA panel. We have assigned Comprehensive Metabolic Panel (14), Test Code #322000 to this request. If this is not the testing you wished to receive on this specimen, please contact the LabCorp Client Inquiry/Technical Services Department to clarify the test order. We appreciate your business.

01	SO	LabCorp San Diego 13112 Evening Creek Dr So Ste 200, San Diego, CA 92128-4108	Dir: Jenny Galloway, MD
02	BN	LabCorp Burlington 1447 York Court, Burlington, NC 27215-3361	Dir: William F Hancock, MD
03	UY	Esoterix Coagulation Lab 8490 Upland Drive Ste 100, Englewood, CO 80112-7116	Dir: Brian F. Poirier, MD
04	NEWXW	Viracor Eurofins 1001 NW Technology Drive, Lees Summit, MO 64086-5603	Dir: Michelle Altrich, PhD

For inquiries, the physician may contact **Branch: 800-859-6046 Lab: 858-668-3700**

https://www.medscape.com/viewarticle/893900?src=wnl_edit_tpal&uac=53825PT

Many Breast Cancer Patients Not Receiving Genetic Evaluation

Roxanne Nelson, RN, BSN March 14, 201

A substantial number of breast cancer patients who could benefit from genetic testing are not being tested, and many others are not being counseled.

A new study shows that in a large cohort of more than 1700 early breast cancer patients, 47.4% were not tested. Although the majority of patients did report having some type of genetic discussion, only half of those who were not tested received any discussion about genetics.

The study was published online March 12 in the *Journal of Clinical Oncology*.
"Patients diagnosed with breast cancer need comprehensive patient-centered communication and decision making," said study author Steven J. Katz, MD, MPH, professor of general medicine and of health management and policy at the University of Michigan, Ann Arbor.
He explained that the "whole process needs to be slowed down, as too often its considered a medical emergency, especially by patients.

"Both patients and doctors need time to collect all the information, including genetic predisposition, in those at higher pretest risk of mutations," Katz told *Medscape Medical News*. "Doctors need to be better trained at counseling and integrating genetic counseling into treatment decisions. Treatment of cancer is largely focused on the biological subtype of the diagnosed cancer, while genetic predisposition plays a much smaller role in surviving cancer."
The authors note that genetic counseling is indicated for breast cancer patients who have an elevated pretest risk of harboring a pathogenic mutation. About one third of newly diagnosed patients do have a higher risk for a genetic mutation, as determined on the basis of their having a family history of cancer, their ancestry, and/or tumor characteristics.
But as testing is becoming more extensive, genetic risk evaluation — including counseling and genetic testing — is currently chaotically deployed into practice, Katz noted.
"Cost is not generally a problem, because the cost of testing is decreasing very quickly. The problem is the clinical utility of the testing today for patients with breast cancer, as there is legitimate clinical uncertainty about its role in treatment decision making," he said.

Testing and Counseling Uneven

Katz and his colleagues note that ideally, counseling should take place prior to surgery, because bilateral mastectomy is one of the options for risk reduction in this population. But putting genetic counseling into practice can be challenging, they note.

Information about integrating genetic counseling into community practices for newly diagnosed breast cancer patients is limited. In this study, they examined the patterns and correlates of discussion along with patient assessments about the information they received.
Surveys were sent to a large, diverse population of women aged 20 to 79 years with favorable-prognosis breast cancer who were identified from the SEER database of Georgia and Los Angeles County as having newly diagnosed ductal carcinoma in situ or invasive breast cancer. The surveys were linked to SEER

clinical data and genetic test results. The cohort available for analysis included 1711 women with indications for formal genetic risk evaluation.
Of the women who were tested, 29.7% only received testing for *BRCA1/2*; 22.9% underwent a multigene panel test (representing 43.5% of those tested).
Of the patients who underwent testing, 14.0% received results indicating "variant of unknown significance (VUS)" only, and 8.6% were found to have a pathogenic mutation. The remainder (77.4%) received negative results.
Overall, nearly three quarters (74.6%) of the cohort received some type of genetic counseling: 43.5% received formal counseling, and 31.1% had a physician-directed discussion.
Genetic counseling was far less prevalent among those who were not tested. Only 22.6% received some type of formal counseling, and 28.0% had a physician-directed discussion. Conversely, almost all patients who were tested reported that they had received some form of genetic counseling (96.4% of those whose test results were negative, and 94.9% of those whose results indicated pathogenic mutations or VUS). About two thirds reported having received formal counseling (60.5% of those with negative test results, and 67.9% of those with pathogenic mutations or VUS).

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Breast Cancer

Gaps in Receipt of Clinically Indicated Genetic Counseling After Diagnosis of Breast Cancer

Steven J. Katz, **Kevin C. Ward**, **Ann S. Hamilton**, **M. Chandler Mcleod**, **Lauren P. Wallner**, **Monica Morrow**, **Reshma Jagsi**, **Sarah T. Hawley**, and **Allison W. Kurian**Steven J. Katz, M. Chandler Mcleod, Lauren P. Wallner, et al

Abstract

Purpose

Little is known about the extent to which genetic counseling is integrated into community practices for patients newly diagnosed with breast cancer. We examined the receipt of clinically indicated genetic counseling in these patients.

Patients and Methods

We surveyed 5,080 patients between the ages of 20 and 79 years, diagnosed from July 2013 to August 2015 with early-stage breast cancer and reported to the SEER registries of Georgia and Los Angeles County. Surveys were linked to SEER clinical data and genetic test results. The study sample (N = 1,711) comprised patients with indications for formal genetic risk evaluation.

Results

Overall, 47.4% did not get tested, 40.7% tested negative, 7.4% had a variant of uncertain significance only, and 4.5% had a pathogenic mutation. Three quarters (74.6%) received some form of genetic counseling (43.5%, formal counseling and 31.1%, physician-directed discussion).

Virtually all tested patients (96.1%) reported some form of genetic discussion (62.2%, formal counseling and 33.9%, physician-directed discussion). However, only one half (50.6%) of those not tested received any discussion about genetics. Younger women were more likely to report some type of counseling, controlling for other factors: odds ratio, 4.5 (95% CI, 2.6 to 8.0); 1.9 (95% CI, 1.1 to 3.3); and 1.5 (95% CI, 1.0 to 2.3) for women younger than 50 years of age, 50 to 59 years of age, and 60 to 69 years of age versus those 70 years of age and older. Patients' assessments of the amount of information they received about whether to get tested were similarly high whether they were counseled by a genetics expert or by a physician only (80.8% *v* 79.4% stated information was just right, $P = .59$).

Conclusion

Less than one half (43.5%) of patients with clinical indications received formal genetic counseling. There is a large gap between mandates for timely pretest formal genetic counseling in higher-risk patients and the reality of practice today.